Attorney Docket No. 9052-67 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001
Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

Commissioner for Patents
Post Office Box 1450
Alexandria, Virginia 22313-1450

DECLARATION UNDER 37 C.F.R § 1.132
OF ANDREW BARRETT

Sir:

I, Andrew Barrett, do hereby declare and say as follows:

1. I am currently the Director of Business Development and Licensing for Innovata Limited/ Vectura Group plc. I have held this position since July 2004 and have been involved with Adept® since the present application was filed. I was responsible for the UK launch of Adept® in May 2000 and subsequent licensing of European-wide rights of Adept® to Shire Pharmaceuticals in October 2001 and for the re-licensing of Adept® on a global basis to Baxter Healthcare Corporation in January 2006. A *curriculum vitae* is attached herewith at Tab 1.

2. Adhesions are the most frequent complication of abdominal surgery and are an almost inevitable occurrence after most abdominal and pelvic surgery. They are a recognised risk of a planned therapeutic intra-peritoneal procedure Tab 2, De Wilde Future Directions in Surgery 2006, March page 30 2nd column "An Urgent Need for

Adhesion Reduction"). As well as the important clinical burden associated with adhesions, the economic burden to healthcare systems is substantial. In 1994, it was estimated that the cost in the US of all hospitalisations for adhesiolysis (surgery to remove adhesions) was US$1.33 billion and of that, US$764 million were for hospitalisations directly attributable to adhesions (Tab 2, page 28, 2nd column "Cost of Adhesions" attached hereto). Furthermore, it is estimated that adhesion formation occurs in 75-90% of patients following major gynaecologic surgery. Six percent of all hospital readmissions result from adhesions; 22% occur in the first year of surgery (Tab 3, Luciano, page 1 "Introduction", appended hereto and also available at http://www.obgyn.net/Frontiers_in_Reproductive_Medicine/Adhesions.asp). It is a well established fact that adhesions are a ubiquitous problem and that they present a significant drain and cost to the healthcare system. There has been a long felt need for an effective adhesion reduction agent, especially since pharmacologic therapies have been shown to be ineffective.

3. Results from a survey of surgeons in 2002, showed that there were four key desirable properties for their ideal adhesion reduction agent; (i) safety; (ii) ease of use; (iii) efficacy and (iv) cost (Tab 4 slides 5 and 6 attached herewith show a slide excerpt from a presentation by Dr Michael Parker BSc MS FRCS FRCS(Ed) on 24 April 2004 "The Modern Management of Adhesions" it is also available at www.euuzlet.hu/koloproktologus/2004/parker.ppt).

4. Adept® is the registered trademark of the commercially available product of a 4% solution of icodextrin used in post-operative adhesion reduction as defined in the present application.

5. A number of different adhesion reduction agents have been proposed over the years and they can broadly be divided into those that are termed as "site specific" or have "broad coverage". The "site specific" agents act as physical barriers or films separating tissues in the body and the three products available to the US surgeon are Preclude®,

Interceed®, and Seprafilm®. Preclude® is not, however, approved for adhesion reduction by FDA. Both Interceed®, and Seprafilm® are approved only for open surgery (laparotomy); and not for laparoscopic surgery. The US indication for Interceed® is: "as an adjuvant in open (**laparotomy**) gynecologic pelvic surgery for reducing the incidence of postoperative pelvic adhesions after meticulous hemostatis is achieved consistent with microsurgical principles.". The US indication for Seprafilm® is: "for use in patients undergoing abdominal or pelvic **laparotomy** as an adjunct intended to reduce the incidence, extent and severity of postoperative adhesions between the abdominal wall and the underlying viscera such as omentum, small bowel, bladder, and stomach, and between the uterus and surrounding structures such as tubes and ovaries, large bowel, and bladder.".

The major disadvantages associated with Preclude® are that it has to be sutured into place, it is understandably difficult to use via laparoscopy, it is non-degradable and thus requires a yet further surgical procedure to remove it from the body, and has limited applicability in peritoneal surgery. It is expensive. These disadvantages are listed in Tab 4 slide 19, Tab 5 Geoffrey Trew, The Obstetrician and Gynaecologist, Vol 6, No 2, 2004, page 1 also available at http://onlinetog.org/cgi/reprint/6/Supplement/1, Tab 6, Tulandi & Al-Sunaidi OBG Management, May 2007, 19:86-94, Table 2 page 88 and Tab 7, De Wilde et al Gynecol.Surg. 2007, 4:243-253, Table 2, page 245 and page 246 1st column, 1st paragraph). Interceed® and Seprafilm® are both resorbable and so overcome the issue of having a second invasive operation for removal, however neither are considered easy to handle by surgeons (Tab 4 slides 9 and 10 and Tab 7, page 246 1st column). Moreover, Interceed® has the highly undesirable disadvantage of being incompatible with blood, its efficacy being reduced in the presence of blood which is something hard to avoid in surgery. SprayGel® is the most complex agent to use as it may require up to 5 kits excluding an airpump. It is not approved in the US and a regulatory study was halted prior to completion. It is apparent from the foregoing that the "site specific" agents, even those that have FDA approval, do not meet surgeons' requirements.

Turning now to the "broad coverage" agents, these include Hyskon®, Sepracoat®, Intergel® and Adept® (Tab 4 slide 19). Hyskon® has a less than satisfactory toxicity and safety profile and has not been approved in either Europe or the US for the reduction of adhesion formation post-surgery. Sepracoat® was not approved by FDA due to poor efficacy and Intergel® was withdrawn from the US market due to late onset post-operative pain (Tab 5, page 13, Table 2 and Tab 6 page 91 1st column "Peritoneal instillates"). The performance and properties of Adept® in comparison to other agents is extremely favourably reviewed in Tab 5, page 13, Table 2, Tab 4 slides 14-19 and Tab 7 page 245, 247-248.

Adept® is the only approved adhesion reduction solution (Tab 7 page 247 2nd column): "Adept® (4% icodextrin solution). Adept is the single approved and available adhesion reduction solution that has a sufficiently long intraperitoneal residence to provide coverage throughout the critical period of adhesion formation." Similar remarks were made via press release following FDA approval:

> "*Adept® is the first and only approved fluid-based approach for adhesion reduction in gynaecological laparoscopic adhesiolysis in the United States. Adept is a liquid, which means it can be delivered directly and rapidly to the site through a laparoscopic port during surgery*" (Tab 8, Innovata plc and Baxter Healthcare Corporation press release dated 1 August 2006).

6. Referring back to the surgeons' requirements of (i) safety; (ii) ease of use; (iii) efficacy and (iv) cost; Adept® has a proven safety record and efficacy as evidenced by extensive clinical trials (Tab 9, Baxter Healthcare Corporation Information for Prescribers attached hereto and in particular page 3 "US Clinical Trial Experience" and page 4 "Clinical Studies"). Adept® is easy to use as a single post-operative instillate (Tab 9).

7. Adept® meets the surgeons' criteria for an ideal adhesion reduction agent. It has also fulfilled a long-felt need as evidenced by the following comments:

In response to a US-conducted phase III clinical trial (Tab 10, ML Laboratories plc Research Update press release dated 4 April 2005) Geoffrey Trew, MRCOG, Consultant in Reproductive Medicine and Surgery at Hammersmith Hospital, London, UK commented as follows:

> *"This is the biggest and best conducted study ever undertaken with an anti-adhesion agent and I find the results very exciting.* ***Adept is one of the most important surgical device developments in the last decade, filling a niche where there is currently nothing at all.*** *It is safe, easy to use and inexpensive, and these study results have confirmed what many people suspected - that is an effective agent".*

In response to FDA approval (Tab 8, Innovata plc and Baxter Healthcare Corporation press release of 1 August 2006 and Tab 11 press release 1 November 2007), Thomas Lyons, Director, Center for Women's Care and Reproductive Surgery, Atlanta, GA and Clinical Assistant Professor, Department of OB/GYN, Emory University Medical School, Atlanta, GA, who served as one of the investigators for the US trial said:

> *"This is a* ***significant development*** *for patients with adhesion–related disorders and the surgeons who are managing those patients" .. . "This is currently the only product which has approval for laparoscopic use, making it doubly helpful since laparoscopic surgery is a better solution for adhesions than traditional open surgery. As a gynaecologic surgeon who works in this area I am excited for our patients and look forward to* ***improved outcomes for our patients***".

> "*Solutions used to address adhesions in the past have been largely ineffective, and none have been approved by the FDA for use in laparoscopic procedures. An effective adhesion-reduction agent like Adept that is approved for use in laparoscopic procedures* ***provides a major clinical benefit***."

In response to the announcement of a global licence of Adept® Adhesion Reduction Solution to Baxter International Inc (Tab 12, Innovata plc press release dated 3 January 2006), Gordon Sutherland, General Manager for Baxter's Biosurgery Business is quoted as saying:

"*We believe this technology offers significant potential for growth globally and addresses* ***a market that has been underserved for some time***".

8. Adept® has been approved and available in Europe since 2000 as a 4% icodextrin solution used in adhesion reduction. In 2005, the sales were $5,000,000 per annum (Tab 13, ML plc press release dated 21 June 2005). By 2006 it had been already been used in over 100, 000 surgical patients (Tab 10, Tab 14 and Tab 15, Innovata plc press releases dated 28 March 2006 and 1 June 2006 respectively).

9. It is my belief that Adept® has achieved and continues to enjoy considerable commercial success as evidenced by the sales data in Europe and since the launch in USA in November 2006. Adept® is an innovation and is the sole aqueous fluid-based adhesion reduction option for patients: its success is evidenced, at a minimum, by its licensing to two major pharmaceutical companies (the details of these licence agreements cannot, unfortunately, be disclosed). As noted by the licensee, Gordon Sutherland General Manager for Baxter's Biosurgery Business (Tab 12, Innovata plc press release dated 3 January 2006) "*This agreement [the global licence for Adept] adds another platform technology to our BioSurgery portfolio and allows us to enter the anti-adhesion market with a clinically proven product.*".

Furthermore, in a news release from Baxter Healthcare Corporation, six days later, dated 9 January 2006 (Tab 16 and also available at http://www.baxter.com/about_baxter/news_room/news_releases/2006/01-09-06-tricos.html) it is stated :

> *"Baxter's BioSurgery business is focused on developing and commercializing novel biomaterials for hemostasis and hard and soft tissue repair in surgery. In addition to TISSEEL, other products in the BioSurgery portfolio include FLOSEAL® [Hemostatic Matrix] for rapid hemostasis, and COSEAL® [Surgical Sealant], a vascular sealant. With annual sales of approximately $250 million,* ***BioSurgery has become one of Baxter's fastest growing businesses.***
>
> ***The company's accelerated investments in this business have resulted in recent research and development collaborations, including an agreement signed this month with Innovata PLC to acquire a global license for Adept, an adhesion reduction solution for use in obstetric and gynecologic surgery.*** *" (emphasis added)*

10. Baxter is a global enterprise, with approximately 46,000 employees worldwide. At the time of the license agreement, Innovata had approximately 100 employees in UK. In a recent (4 September 2008) investor presentation (5th Annual Goldman Sachs European Medtech and Healthcare Services Conference, attached herewith as Tab 17), the Adept® device technology featured on pages 1 and 3. Clearly the Adept® device technology is an important and lucrative part of Baxter's business.

11. Adept® adhesion reduction solution received a unanimous recommendation for marketing approval by the Obstetrics and Gynaecology Devices Panel of the Medical Devices Advisory Committee of the US Food and Drug Administration (FDA) . The basis of the FDA's approval is shown in Tab 18. Approval date was 28 July 2006 and the link to the Approval letter is http://www.fda.gov/cdrh/pdf5/p050011a.pdf.

12. As stated under point 1 above, Adept® is currently under license to Baxter and a copy of the "Information for Prescribers" issued by Baxter is attached herewith as Tab 9. I would like to emphasise that the Baxter license agreement covers the Adept® product and that the Adept® product is as defined in the claims of the present application. That is to say, Adept® is an aqueous formulation of 4% icodextrin (page 1 "Device Description and Mechanism of Action": and is a dextrin that contains more than 15% of polymers with a degree of polymerisation greater than 12) used as an instillate (page 10 "Directions for Use") for direct intraperitoneal administration (page 1 "Caution" and page 2 "Precautions") into a body cavity for the reduction of post-surgical adhesions in gynaecological operations (page 2 "Indications for Use"). It acts as an osmotic agent (page 1 "Mechanism of Action and Clearance") and performs its function through a separation of tissues which might otherwise adhere together (page 1 "Mechanism of Action and Clearance") and that remains in the body cavity for at least 2 days (page 1 "Mechanism of Action and Clearance").

13. In conclusion, Adept® has fulfilled a long unmet surgical need as a safe, efficient, cost-effective, easy to use adhesion reduction agent. It has achieved widespread use: by 2006 it had been used in over 100,000 surgical patients. It has proved to be a commercial success, for example, with two different major pharmaceutical licensee partners (initially with Shire Pharmaceuticals and currently with Baxter Healthcare Corporation) and it had achieved, by 2005, sales of $5,000,000 per annum.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title

18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

September 26th 2008

Andrew Barrett

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 1

A L Barrett resume

ANDREW BARRETT

Old Hall Cottage, Hall Road, Brandon, Lincolnshire, NG32 2AT
Tel: +44 (0) 1636 626924 Mobile: +44 (0) 7850 300727 E-mail: andrewelan@aol.com

Profile

A sales and marketing/business development and licensing professional with over twenty years experience primarily covering the pharmaceutical and medical devices sectors of the healthcare market. Key areas of expertise include the acquisition and out-licensing of products, relationship management with licensees/licensors, creation and implementation of marketing strategies, opportunity analysis for new products. This is combined with an international network of contacts within the above sectors in industry and the health services.

July 2004 to present — **Innovata PLC/Vectura Group PLC**
Director of Business Development and Licensing

Re-acquired Adept from Shire Pharmaceutical in preparation for global deal. Responsible for re-licensing of Adept on global basis: instrumental in negotiations for agreement concluded with Baxter in late 2005. Responsible for licensing/BD activity for respiratory/pulmonary products ex US/EU with significant experience in Japan and India. Additional activities in seeking partners/licensees for non-respiratory products. Active in search for new development projects, providing strategic analysis of fit for company.

[Note: Innovata was formed in July 2005 after the acquisition of Quadrant by ML Laboratories, Innovata acquired by Vectura Jan 2007]

Nov 1999 to June 2004 — **ML Laboratories PLC**
Marketing Manager/Business Development Manager

Implemented clean-sheet launch of Adept, anti-adhesion liquid. Responsible for all marketing initiatives and hiring of contract sales-team to sell product pending out-licensing. Successfully out-licensed Adept to Shire with bids on-hand from a number of other EU pharma companies. Completed out-licensing deals in Greece, India, Israel, Ireland. In-licensed Alpharen treatment for hyperphosphataemia from Ineos Silicas.

Dec 1995 to Nov 1999 — **Elan Consulting**
Independent sales & marketing consultant

Self-employed consultant working with a variety of healthcare and service industry clients including Glaxo Wellcome, Abbott Laboratories, Ferring Pharmaceuticals, ML Laboratories, AstraTech, CCL, Maersk Medical UK, Maersk Medical A/S (Denmark), Muoviserres Oy(Finland),
Primary activities centred on in/out-licensing, new product development and sales/marketing strategies

A L Barrett resume

July 1993 to Dec 1995 **UnoPlast UK Ltd.**
Sales & Marketing Director

Responsible for sales, product management and new business development relating to the marketing of medical devices. Actual duties involved:-

- management of two direct reports together with two product managers and a sales team of eight representatives. Full management role from recruitment, training and team building perspective including the setting and monitoring of targets
- oversee product management encompassing sales strategy, introduction of new products, pricing and competitor analysis
- new business development including the assessment of new products, establishment of contracts, identification of new clients and successful cross-selling of products so as not to dilute existing market share
- on-going client relationship management through effective customer service and product awareness initiatives with the development of a network of contacts within the hospital sector

Fully accountable for the growth of market-share and the generation of profits. Key negotiator with NHS regions for contracts.

April 1992 to July 1993 **Baxter Biosciences**
Business Development Manager

Responsible for the sales and marketing activities of the northern Biosciences Division of this major healthcare company incorporating the management of a team of 6 technical sales specialists. Actual duties involved:-

- development of marketing plans primarily relating to blood collection products including the identification of new markets and growth strategies.
- responsibility for increase in market share and profit growth with overall responsibility for the effective structuring and negotiation of multi-million pound transactions
- establishment of a joint venture with a major hospital to fund and use new blood cell processing equipment

Dec 1984 to Mar 1992 **Abbott Laboratories Ltd.**

Progressed through Sales and Marketing within this major healthcare company gaining exposure to most aspects of nutrition, medical devices and pharmaceutical products, as follows:-

Mar 1991 Marketing Manager for the hospital products division. Primary achievements were the launches of new medical equipment such as Electronic Flow Equipment and Patient "Pain Control" Equipment

Sept 1989 S.E. Regional Sales Manager for nutritional products and medical equipment (up to 13 representatives)

Nov 1988 New Business Development Manager for pharmaceutical products at international level

May 1987 Appointed Business Development Manager for Antibiotic products. Managed a £2.5m advertising and promotions budget with further responsibility for profit and pricing

Updated 22/09/2008

A L Barrett resume

June 1986 Promoted to Product Manager to determine market strategy relating to cardiovascular products and new initiatives for older brands

Dec 1984 Sales Representative selling antibiotic and cardiovascular products direct to GPs, hospital consultants and high street chemists

July 1992 to Dec 1984 **Sinclair Mcgill Plc**

Responsible for direct sale of agricultural products to farmers in North Lincolnshire.

Personal Details

Married with two sons (15 and 13 years old)

Updated 22/09/2008

A L Barrett resume

QUALIFICATIONS

1982 BSc (Hons) Applied Science (2:1) Sheffield Hallam

1978 3 'A' levels (Chemistry, Biology, General Studies)

1976 11 GCE 'O' levels

OTHER QUALIFICATIONS

1985 ABPI Medical Representatives Exam

1984 NIAB Crop Inspection Certificate

PROFESSIONAL AFFILIATIONS

Pharmaceutical Licensing Group
Aerosol Society
American Association of Gynecological Laparoscopy

PERSONAL DETAILS

Age: 47; Married with two children (14 and 12 y.o.)

Updated 22/09/2008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 2

Report by
Rudy Leon De Wilde

Professor and Head, Department of Department of Obstetrics & Gynaecology, Pinn Hospital

Post-operative adhesions are an almost inevitable occurrence after most abdominal and pelvic surgery procedures, and are a major cause of morbidity and occasional cause of death to patients, as well as a considerable expense to both health systems and society. Adhesions complicate surgery, impacting on successful clinical outcomes. However, most surgeons lack full awareness of the magnitude and consequences of adhesions and thus do not act to reduce their occurrence.

There are several reasons for this:

- The aetiology of adhesion formation remains incompletely understood
- The epidemiology of adhesions has only recently been explored, and the burden they pose is only now understood.
- Adhesive complications can occur unpredictably, sometimes many years after a procedure, and are frequently treated by physicians or specialists other than the initial surgeon
- There is a track record of nearly a century of failure, or limited applicability of traditional adhesion reduction strategies, that lasted until the introduction of newer agents.

This lack of awareness amongst most surgeons of the clinical significance and frequency of adhesion has been cited as the greatest impediment to reducing adhesion formation

This paper will review the need for surgeons to act now to reduce adhesions, and in a separate paper on this issue, following this paper, Geoffrey Trew reviews adhesion reduction options

Adhesions – the Extent of the Problem

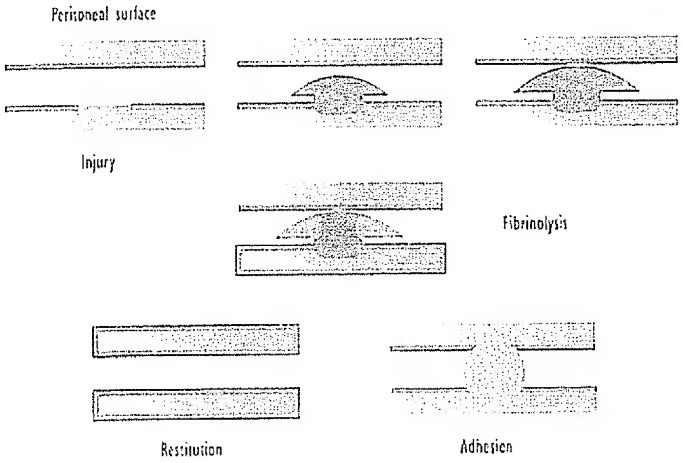
Studies have shown that after laparotomy 93% of patients have adhesions at subsequent surgery. As well as carrying a risk of death from adhesion-related complications, adhesions are a major cause of morbidity and expense. For patients they are the most common pathology associated with chronic pelvic pain, which is a debilitating and complex problem to manage. Seventy-four per cent of small bowel obstructions are adhesion-related and this is the leading cause of intestinal obstruction in developed countries. It is estimated that 20–40% of secondary infertility in women is as a result of adhesions. Even when patients experience no problems with adhesions, they can pose an important complicating factor for surgeons, and thus patients undergoing future surgery. Adhesions from previous surgery significantly increase subsequent operating time by a median of 18 minutes and their presence increases the risk of damage to underlying organs and tissues, which are the commonest cause of successful surgical negligence suits. Even in the hands of experienced surgeons there is a 19% risk of inadvertent enterotomy at re-operative laparotomy and a risk of bowel injury of 10–25% has been reported in laparoscopic adhesiolysis

Formation of Adhesions

Adhesions are abnormal attachments between tissues and organs. They may be congenital or acquired – the latter as a result of a generalised phenomenon in response to trauma to the peritoneum. Triggers for adhesion formation include infection, e.g. appendicitis, chemical irritation, e.g. spillage of the contents of dermoid cysts and endometriosis. In addition, adhesions may be formed following surgical trauma, prompted by events such as exposure to infection/intestinal contents, ischaemia, irritation from foreign materials, e.g. sutures, gauze and glove dusting powder, abrasion, desiccation, overheating by lamps or irrigation fluid

Adhesion formation is a surface event associated with peritoneal wound healing. Abrasion and other trauma lead to disruption of the mesothelium, the surface of which is extremely delicate, as its cells are loosely interconnected. Fibrin is then deposited at the damaged surfaces by bleeding and post-traumatic inflammation. This fibrin mass enlarges, reaching another tissue surface and forming a bridge between the tissue surfaces (see *Figure 1*). Locally generated fibrinolytic factors are released that may degrade all

Figure 1: Pathogenesis of Adhesions



or part of this fibrin bridge. However surgery, infection and hypoxia dramatically diminish fibrinolytic activity and, in this case, fibroblasts and other cells may migrate across the bridge remnants, transforming it from the initially reversible fibrinous adhesion into a permanent adhesion with a connective tissue structure.

While the severity and extent of adhesions may change over weeks and months, the incidence of an adhesion – that is, whether it develops at all – is decided in the three to five days after peritoneal trauma takes place. Importantly, in relation to adhesion reduction, the process of formation begins during surgery.

The Epidemiology of Adhesions

The extent of the problem of adhesions was initially comprehensively identified by the seminal works of Harold Ellis and Don Menzies and studies by other investigators. However, not until the Surgical and Clinical Adhesions Research (SCAR) group investigated the epidemiology was the extent of the burden that adhesions posed to patients, surgeons and the health system properly understood. Their initial study followed adhesion-related hospital re-admissions in Scotland for 10 years in a cohort of patients undergoing open abdominal or pelvic surgery. They found that up to one in three patients were re-admitted at least twice for adhesion-related problems or operations not related to adhesions but potentially complicated by them during this period. They also found that the re-admissions continued steadily through the 10 years. Their research indicated that patients undergoing open surgical procedures on the colon and rectum in general surgery and on fallopian tubes and ovaries in gynaecological surgery were at most risk of adhesion-related re-admissions. An assessment of the prevalence of adhesions demonstrated that adhesion-related admissions were as common in 1994 as hospital admissions for appendectomies, hip replacements and coronary bypass grafts.

Subsequently, the SCAR group also examined more current epidemiology, investigating adhesion-related outcomes following laparoscopy as well as laparotomy. They reported that for therapeutic and diagnostic laparoscopic procedures – in effect all laparoscopic procures undertaken with the exception of low-risk tubal sterilisations, which represented 40% of laparoscopic gynaecology cases – the risk of adhesion-related readmission was at least comparable to gynaecological laparotomy and indeed higher than for the most common form of gynaecological laparotomy – uterine laparotomy. They have shown that, despite advances in surgical technique including laparoscopy, the burden of adhesion-related re-admissions continues. A more recent study by the SCAR group has shown that patients undergoing laparoscopic gynaecological surgery involving adhesiolysis or where previous abdominopelvic surgery has been performed are at higher risk of adhesions.

The Cost of Adhesions

As well as the important clinical burden associated with adhesions, the economic burden to healthcare systems and society is substantial.

A survey in 1993 in Sweden – population 7.1 million – found that total care, including costs for sick leave, for adhesive small bowel obstruction amounted to at least US$13 million per year. The costs in 1994 of all hospitalisations for adhesiolysis in the US were estimated to be US$1.33 billion, of which approximately US$764 million were for hospitalisations directly attributable to adhesions.

Using the SCAR data, the average lengths of hospital stay for adhesion-related general and gynaecological surgery in 1994 showed that treatment costs in that year for adhesion-related surgical procedures were over £6 million, representing 2% of Scottish expenditure on hospital and community sector services in 1994, and this is a conservative estimate of actual costs. A subsequent cost model based on the SCAR data predicted that the direct annual cost of adhesion-related readmissions for the UK within the first year after initial lower abdominal surgery would be in excess of £24.2 million, rising to £95.2 million in the 10th year after surgery. The model estimated that the cumulative year-on-year direct costs of adhesion-related readmissions for a 10-year period would be more than £569 million for a population of 56 million.

Extrapolating these cost data to a global scale clearly shows that adhesion-related problems represent a huge burden within healthcare resources and funding – let alone the overall cost to society, as well as the individual patient

Moreover, medicolegal litigation resulting from adhesion-related complications is rising, adding to the costs to health systems and the clinician's burden

Which Adhesions Cause Most Problems?

While is not possible to identify which adhesions will create complications, logic and clinical observation indicate that those involving key organs and tissues such as the small intestine or adnexa, are the most likely to be symptomatic. In the treatment of adhesion-related small bowel obstruction outcomes following conservative treatment have been shown to be worse if adhesions are a result of previous appendectomy, tubal or ovarian surgery

Medicolegal Considerations

Adhesions remain a common consequence of surgery with serious health implications for patients including small bowel obstruction, infertility and chronic pelvic pain. Even if adhesions are 'silent', posing no issues for the patient, the risks of complications at re-operative surgery are considerable

Tissue damage to underlying structures during laparoscopic surgery has been shown to be the most common cause of successful surgical negligence suits[35] and it is estimated that there is a 10–25% risk of bowel injury in laparoscopic adhesiolysis cases and a 19% risk of inadvertent enterotomy during re-operative laparotomy. Furthermore, in a study of misadventure data following laparoscopic surgery, while injury to the common bile duct was the most frequent, perforation of the small bowel or colon was the second most common injury, and two-thirds of injuries were initially missed and not recognised until after conclusion of the surgical procedure. Risk of damage was greater when there were difficulties visualising structures which can be a common issue with adhesions

In the period between 1994 and 1999, the UK Medical Defence Union received 77 adhesion-related claims and there were out-of-court settlements in 14 cases in 11 years, ranging from £7,960 to £124,261 – an average of £50,765 per case

The most common reasons cited were:

- failure to diagnose adhesion-related problems;
- delay in diagnosis;
- bowel damage at adhesiolysis;
- infertility or risk of infertility;
- starch granuloma – use of starch-powdered gloves; and
- failure to take precautions to prevent adhesions.

This was until 1999. Since then, evidence on the epidemiological and economic burden of adhesions and the risk to patients has expanded considerably, and it is clear from recent work by SCAR-2 and SCAR-3 that there has been little change in the epidemiology of adhesions even with advances in surgical techniques – in some instances laparoscopic surgery appears to be as adhesiogenic as open surgery – if not more so

Along with this rise in our scientific and clinical understanding of adhesions, there have also been new developments in anti-adhesion agents and our practical knowledge of using them – as Geoffrey Trew discusses in the following paper. Not all agents are difficult or costly to use and there is now promising evidence of efficacy not only in reduction of adhesions but in subsequent outcomes

An Urgent Need for Adhesion Reduction

Considering the mounting experience and evidence of post-operative adhesions and their impact, and in the face of new developments in anti-adhesion agents, it is clear there is a need to routinely implement adhesion reduction strategies including use of anti-adhesion agents. With the wealth of evidence of the risks of adhesions forming after all types of surgery and in the knowledge of the extent of the problems they lead to, the time is coming when not to advise patients as part of the consent process that there is a recognised risk of adhesions from a planned therapeutic intra-peritoneal procedure and not to take action to reduce adhesions, including use of adhesion reduction agents, could be considered potentially negligent. Indeed this is a matter of considerable and broadening discussion, with recent expert reviews in the Germany and the UK recommending action to reduce adhesions through good surgical technique and routine use of safe and effective anti-adhesion agents, particularly during high risk surgery.

A version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchbriefings.com)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 3

OBGYN.net
The Universe of Women's Health

FRONTIERS IN REPRODUCTIVE MEDICINE

ARTICLES AND PRESENTATIONS FROM WORLD EXPERTS ON THE FRONTIERS IN REPRODUCTIVE MEDICINE

ABOUT THE EDITOR

Carmen Sevilla, MD

Special Minimally Invasive Surgery

TABLE OF CONTENTS

Adhesion Formation and Prevention

Danielle Luciano, MD
Center for Fertility and Women's Health, New Britain, CT

Adhesion formation occurs in 75-90% of patients following major gynecologic surgery. Six percent of all hospital readmissions result from adhesions; 22% occur in the first year after surgery, costing 1.3 billion dollars a year. Adhesions cause pelvic pain, infertility, bowel obstruction and difficult repeat surgery. Forty percent of all repeat surgeries are complicated by adhesions.

This article will review the pathophysiology of adhesion formation and preventative measures that can be taken to minimize adhesion reformation and de novo adhesion formation.

Pathophysiology of Adhesions

Adhesions are abnormal attachments of tissue surfaces that are consequences of the natural healing process. Surgical tissue trauma (mechanical, thermal, desiccation, infection, ischemia, abrasion, radiation) initiates a cascade of inflammatory events to heal the injured tissue. Vasoactive substances and inflammatory exudates are released and fibrous scars form over the injured area. Normally within three days these scars are broken down by a process of fibrinolysis. If peritoneal trauma is too severe or this fibrinolytic process does not occur, more fibrin is deposited and capillary development occurs, leading to permanent adhesion formation.

Pelvic pain resulting from adhesion formation is poorly understood as some patients with extensive adhesions will have minimal pain and some patients with minor adhesions will have severe pain. Pain may be associated with tension or stretching of adhesions on the organs; immunohistochemical studies have demonstrated the presence of nerve fibers in adhesions. Location of adhesions seem also to predict pain as adhesions involving the bowel seem to cause more pain than adhesions at other sites. Studies suggest that pain can be reduced by 40-90% following adhesiolysis in pelvic pain patients with adhesions as the only pathologic finding.

Adhesions are the cause of infertility in 15-20% of patients. Adhesions around the ovary can affect follicular growth, and peritubal adhesions can affect tubal motility and ovum transport. Adnexal adhesions also increase the risk of ectopic pregnancy. Studies suggest adhesiolysis in patients with adhesion related infertility can result in pregnancy rates of 38-52% [1]

Adhesions cause about 70% of all bowel obstructions; 20% occur in the first month after surgery. A review of hospital admissions for small bowel obstruction at a university hospital in Canada looked at antecedent gynecologic surgeries and percent occurrence of small bowel obstruction (SBO). Total abdominal hysterectomy was associated with the highest rate of SBO (1.4%) followed by

open adnexal surgery (0 81%). In this study there were no SBO following laparoscopic surgery

One complication of adhesions not often considered is difficulty during repeat surgeries. Studies done by colorectal surgeons demonstrated increased OR time of 18 minutes per previous surgery and increased risks of inadvertent enterotomy and conversion from laparoscopy to laparotomy [1] Complex repeat surgeries, as well as pelvic pain, infertility and increased risk of bowel obstruction reinforce the need to attempt to minimize adhesion formation following surgery

Prevention of Adhesions

Adhesions form following the majority of gynecologic procedures. Measures that have been developed attempting to prevent adhesions include: proper surgical technique, pharmacologic treatment, and surgical barriers. Minimally invasive surgical technique with meticulous hemostasis is essential to avoid unnecessary peritoneal injury. The surgeon should avoid excessive coagulation of tissue that can lead to ischemia, and avoid foreign body contamination with extra suture material and powdered gloves. A statistically significant decrease in adhesion reformation and de novo adhesion formation was seen in studies comparing laparoscopy with laparotomy.

Pharmacologic therapies have been studied for efficacy in reducing adhesion formation and unfortunately have not been shown to be effective. Both local and systemic NSAID and corticosteroids have been studied with no difference in adhesion formation
Antibiotics both intravenous as well as used as peritoneal instillates have not been shown to be effective, and neither has heparin as a peritoneal lavage or left in situ. Streptokinase has been tried as well with no efficacy. This has led to the ASRM Practice committee to recommend not using anti-inflammatory agents and peritoneal instillates as they have not demonstrated benefits for reducing postoperative adhesions.[2]

Surgical barriers have been developed to reduce adhesion reformation, and they have been found to be effective. Gortex, Interceed, and Seprafilm have been approved by the FDA for use in laparotomy and have been found to be effective in reducing adhesion reformation. Adept, an isotonic 4% icodextrin solution, is the only adhesion barrier approved by the FDA for use with laparoscopy and has been shown to reduce adhesions by approximately 30% compared to lactated ringers

A recent study looking at adhesion reformation following laparoscopic adhesiolysis suggests that adhesions that reform are more likely to occur on the adnexa and that new adhesions were more likely to be dense, involve less than one third of the organ, and occur on the adnexa as well. Endometriosis did not seem to affect the reformation of adhesions however a greater percentage of patients without endometriosis had de novo adhesion formation than patients with endometriosis

Preventing adhesions especially around the adnexa is important in gynecologic surgery to avoid the consequences of pelvic pain, infertility, bowel obstruction and difficult repeat surgery. Consequently I would like to strongly echo the ASRM practice committee recommendation that efforts to minimize adhesion formation should be implemented, and they should include not only minimally

invasive surgical techniques with excellent hemostasis but also the proper use of effective adhesion reducing surgical devices

[1]Davey AK, Maher PJ. Surgical adhesions: a timely update, a great challenge for the future. J Min Inv Surg. 2007;14(1):15-22.

Practice Committee of the American Society of Reproductive Medicine. Control and prevention of peritoneal adhesions in gynecologic surgery. Fert Ster 2006;86(4):S1-S5

[2]Kligman I. Immunohistochemical demonstration of nerve fibers in pelvic adhesions. Obstet Gynecol. 1993; 82(4):566-8

Steege JF. Resolution of chronic pelvic pain after laparoscopic adhesiolysis. Am J Obstet Gynecol. 1991, 165(2):278-81.

Al-Sunaidi M, Tulandi T. Adhesion-related bowel obstruction after hysterectomy for benign conditions. Obstet Gynecol. 2006;108(5):1162-6

[3]Luciano AA, Maier DB, Nulsen JC, Whitman GF, Koch EI: A comparative study of postoperative adhesion formation following laser surgery by laparoscopy versus laparotomy in the rabbit model. Obstet Gynecol. 1989;74:220-224.

[4]Luciano AA, Montanino-Oliva M. Comparison of postoperative adhesion formation laparoscopy versus laparotomy. Infertil Reprod Med Clinics N Amer. 1994;5(3):437-44.

[5]DeCherney AH, Chang WY, Marin CM. Preventing adhesions after abdominal myomectomy: tools and techniques. OBG Management. 2003;6:18-37

[6]Brown CB, Luciano AA, Martin D, Peers E, Scrimgeour A, diZerega GS. Adept (icodextrin 4% solution) reduces adhesions after laparoscopic surgery for adhesiolysis: a double blind, randomized, controlled study. Fert Ster. 2007;88 (5):1413-26.

[7]Luciano DE, Roy G, Luciano AA. Adhesion reformation after laparoscopic adhesiolysis: where, what type, and in whom they are most likely to recur. J Min Inv Surg. 2008 in press

[8]Practice Committee of the American Society of Reproductive Medicine. Pathogenesis, consequences and control of peritoneal adhesions in gynecologic surgery. Fert Ster. 2007;88(1):21-6

We encourage readers to [illegible] *with their comments and questions.*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 4

The Modern Management of Adhesions

Michael C Parker BSc MS FRCS FRCS(Ed)

Darent Valley Hospital
Dartford, Kent, UK

SCAR Panel Member

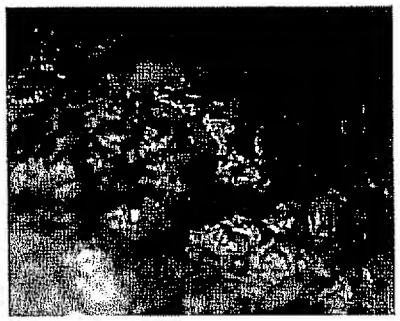
Hungary 24th April 2004

Paradox of surgery…

…the method proposed to treat adhesions is the one that induces adhesions

Need for clinical & cost-effective agents to reduce adhesion development

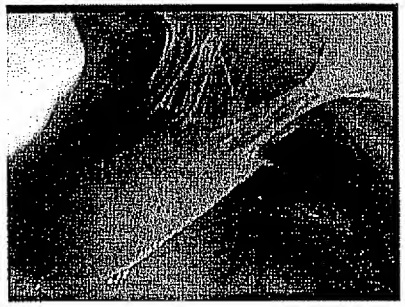
Formation of Adhesions



Injury

Bleeding
Inflammation

Fibrin deposition



Adhesions

Influencing factors during surgery

- Ischaemia
- Infection
- GI contents
- Abrasion
- Desiccation
- Heat
- Light
- Electrocautery
- Sutures
- Fibres
- Glove powder

Adhesion reduction strategies

- Careful surgical technique
- Minimise Inflammatory response
- Augmentation of fibrinolysis
- Adhesion-reduction agents

Adhesion Reduction Agents: The ideal agent

According to recent surveys of surgeons the four key attributes are:

- Safety
- Easy to use
  - General surgery
  - Gynaecological surgery
  - Open
  - Laparoscopic
- Efficacy
  - Operation site
  - Throughout the cavity
- Economical

ESHRE 2002 Survey, EACP 2002 Survey

Adhesion Reduction Agents

Key issues

- Toxicity
- Handling
- Limited efficacy
- Clinical outcomes
- Cost

Adhesion Reduction Agents

Site Specific

Preclude*	expanded polytetrafluoroethylene Gore-Tex sheet	Generally unavailable
Interceed	oxidised regenerated cellulose fabric	
Seprafilm	hyaluronic acid carboxymethylcellulose film	
SprayGel	polyethylene glycol hydrogel	
SurgiWrap	copolymer 70:30 Poly(L-lactide-co-D, L-lactide) sheet	

Broad Coverage

Crystalloids	Ringer's lactate/saline +/- Heparin	
Hyskon	32% dextran 70 solution	Generally unavailable
Sepracoat	0.04% hyaluronic acid-phosphate-buffered saline	Withdrawn
Intergel	0.5% ferric hyaluronate gel	Withdrawn
Adept	icodextrin 4% solution	

* Withdrawn from US market

Most Widely Used Adhesion Prevention Adjuvants

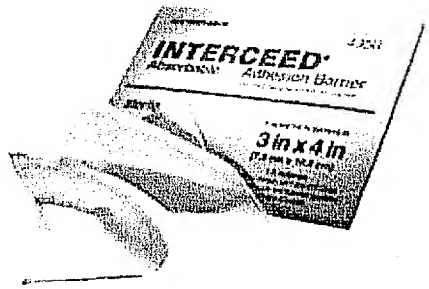
- **Crystalloid instillates**
  - Lactated Ringer's
  - Saline
  - Hartmann's Solution

- **Limitations:**
- Absorbed within 24 hours
- They don't prevent adhesions!

Interceed Barrier

(Oxidized Cellulose, Gynecare)

- First FDA approved adhesion reduction adjuvant
- Most clinical studies (24)
- Widely applicable
  - all intraperitoneal locations
  - all surgical procedures
- Compatible with laparoscopy
- Limited use in colorectal surgery



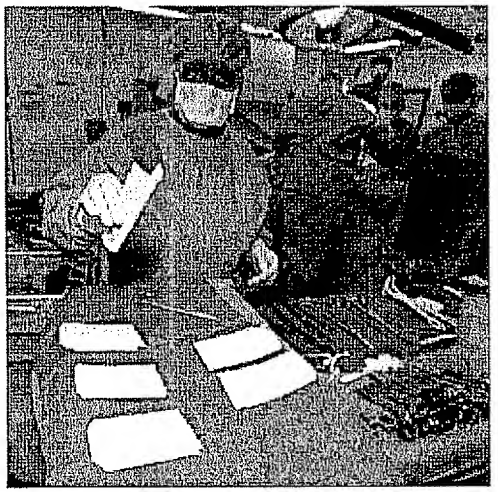
Limitations:

- Blood oozing renders it ineffective
- Irrigants must be removed
- Technical application challenges!

Seprafilm Membrane

(HA+CMC, Genzyme)

- Widely applicable
  - covers all intraperitoneal locations
  - all surgical procedures
- Used in general surgery



Limitations:

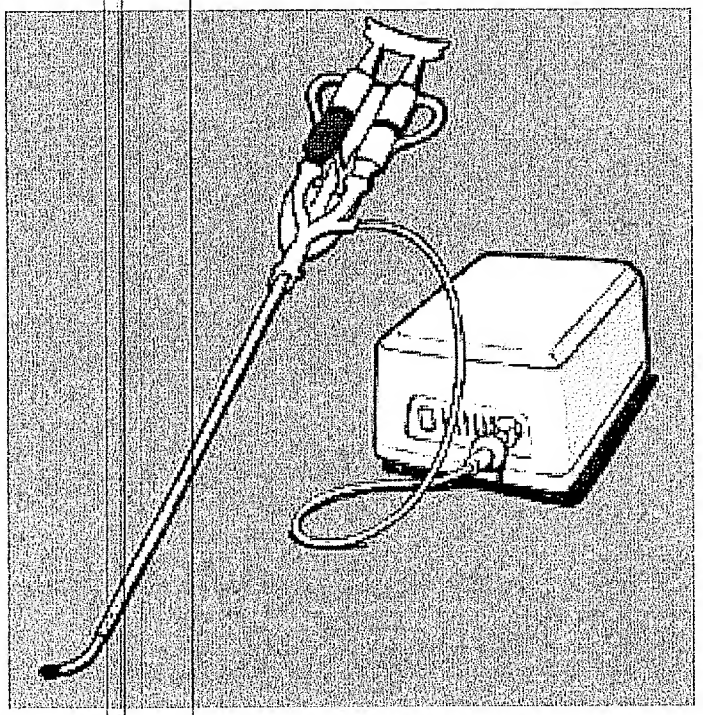
- Handling
- Residual irrigation fluid must be removed
- Cannot be used via laparoscopy
- Cannot use at site of anastomosis
- Cost!!
  - need mean 4.4 sheets in colorectal surgery!!!*

Beck et al Dis Colon Rectum 2003;46:1310-1319

SprayGel

Limitations

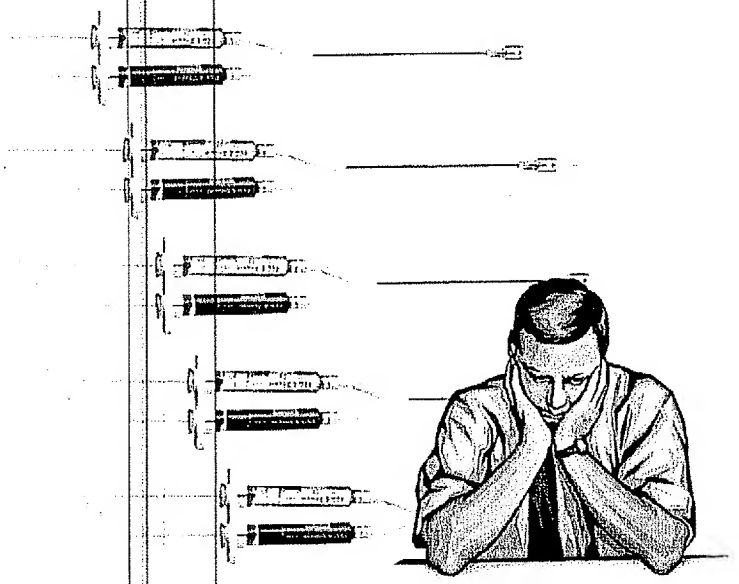
- complex set-up
- time consuming
- limited efficacy & safety data
- US regulatory study halted
- cost……



SprayGel

Limitations

- complex set-up
- time consuming
- limited efficacy & safety data
- US regulatory study halted
- cost……
  - –particularly 5 kits!*

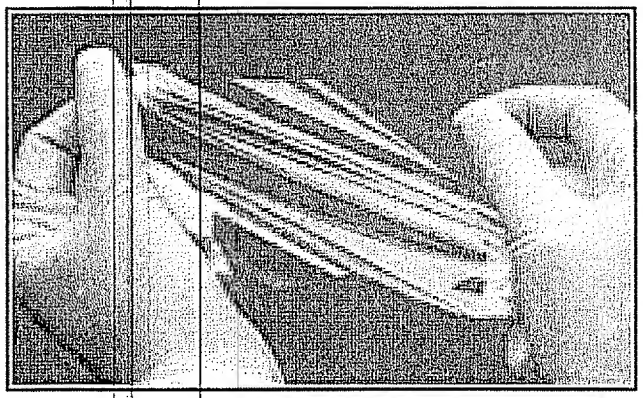


*Korell Adhesions News & Views 2004 in press

SurgiWrap (13)

(polylactide copolymer film, Macropore)

- Peritoneal replacement film
- Suture in place
- Remains for ~6 months
- Excreted through lungs



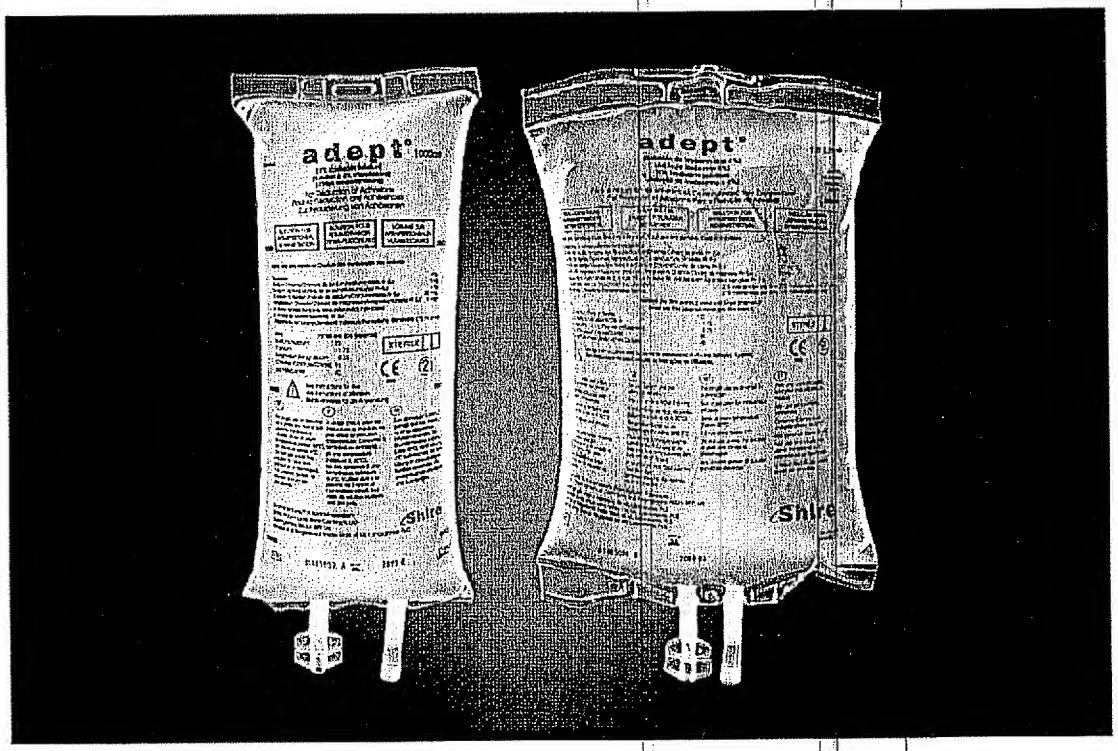
Limitations:

- Data – limited safety and efficacy
- Handling??
- Cost!!

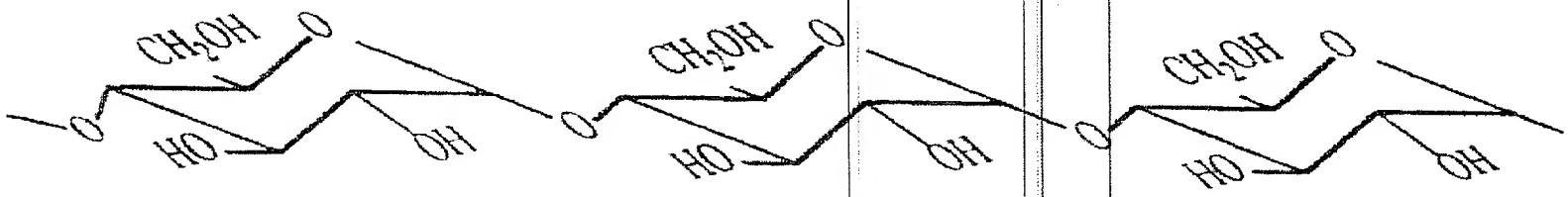
14

Adept®

New solution to adhesion reduction?

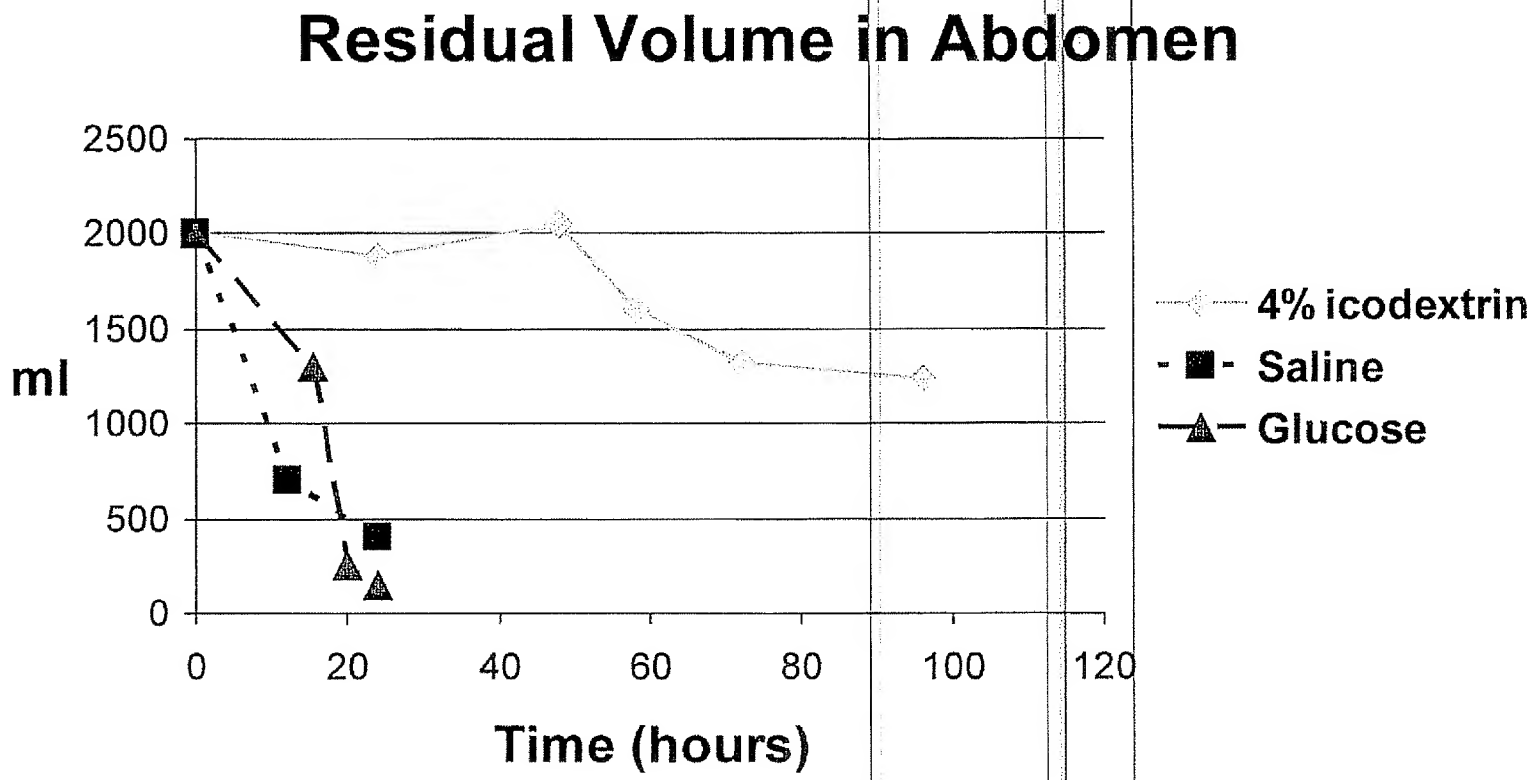


Adept - icodextrin 4% solution



- α 1,4 linked glucose polymer
- Icodextrin 4% solution
  - isosmolar
  - biocompatible
  - well-established safety profile at 7.5% concentration
  - >36,000 patient years safety data from renal use
  - ~50,000 patients treated with Adept
  - persists in peritoneal cavity
  - reduces adhesion formation through physical action
  - **'hydroflotation'**

Adept hydroflotation mechanism



Hosie et al Drug Delivery 2001

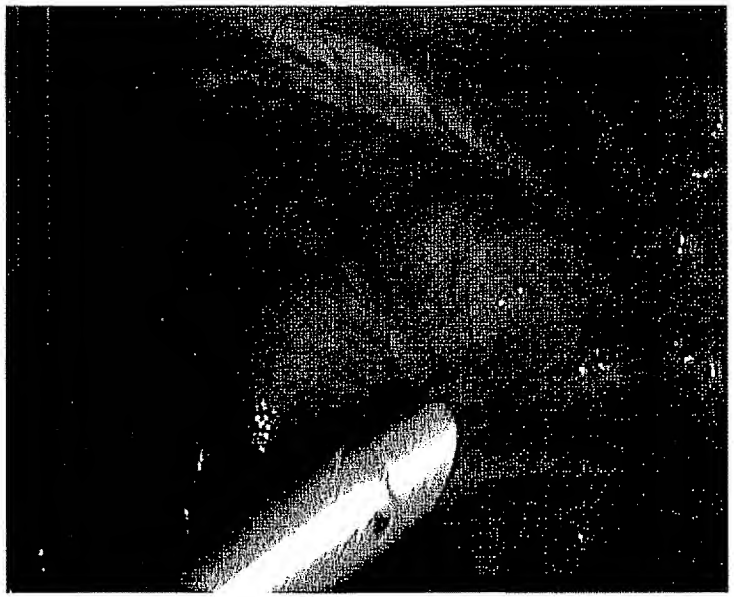
Adept use

17

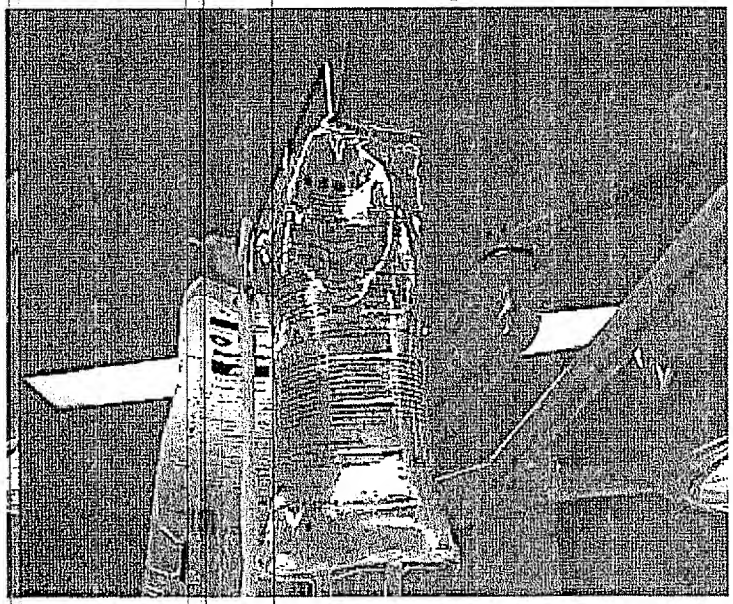
- **Irrigation** - minimum 100mls/30mins
  - Laparoscopy through the scope
  - Laparotomy via a syringe

- **Instillation** - 1000ml at closure

Laparoscopy



Laparotomy



Adept

(Icodextrin 4%, Shire Pharmaceuticals)

- Used as an irrigant and an instillate
- Covers all intraperitoneal locations
- Easy to use
  - laparoscopic clinical studies
  - laparotomy registry feedback
- Not constrained by oozing
- Residual irrigation solution is not a problem
- Extensive safety experience at 7.5%
- ARIEL Registry of routine use in >4,600 patients
  - feedback of use and safety good
- Promising early results
- Modest cost

Limitations:

- Limited clinical data at present – extensive work in progress

Surgical procedures and adjuvant use

	Adhesion Type		Fertility Surgery				Gynaecology				General Surgery	
	De novo	Reform	Open		Laparoscope		Open		Scope		Open	Scope
			Uterus	Adnexa	Uterus	Adnexa	Uterus	Adnexa	Uterus	Adnexa		
Site Specific												
Preclude	+++	+++	√	X	X	X	√	X	X	X	√	X
Interceed	+++	+++	√	√	√	√	√	√	√	√	O	O
Seprafilm	+++	+++	√	X	X	X	√	X	X	X	√	X
SprayGel	+++	+++	√	√	√	√	√	√	√	√	?	?
SurgiWrap	?	?	?	?	?	?	?	?	?	?	?	?
Broad Coverage												
Hyskon	++	++	O	O	O	O	O	O	O	O	O	O
Sepracoat	++	++					**Withdrawn**					
Intergel	+++	+++					**Withdrawn**					
Adept	+++	+++	√	√	√	√	√	√	√	√	√	√

O = not used/recommended

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 5

www.rcog.org.uk/tog

The Obstetrician & Gynaecologist

the journal for continuing professional development from the Royal College of Obstetricians and Gynaecologists

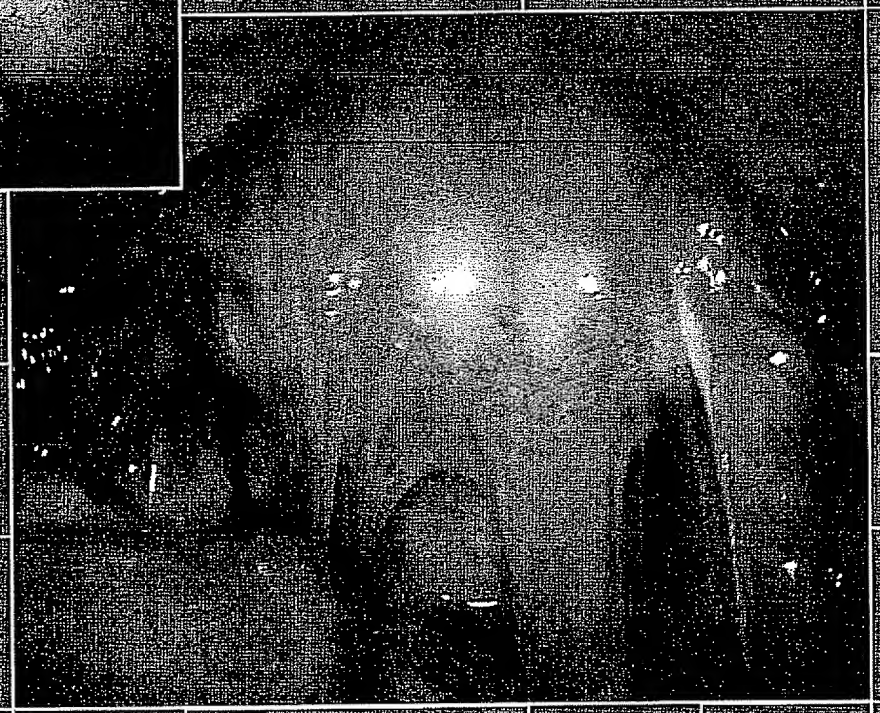
SUPPLEMENT Volume 6 Number 2 2004

Consensus in adhesion reduction management

by Geoffrey Trew MRCOG

Consultant in Reproduction Medicine and Surgery, Hammersmith Hospital, London, UK and Honorary Senior Lecturer, Imperial College, London, UK

Guest Editor: Adrian Lower FRCOG



RCOG PRESS

The Obstetrician & Gynaecologist
2004;6(2)
SUPPLEMENT

Adhesion Prevention Strategies

Adhesions substantially increase workload and have a major impact on healthcare resources. With an increasing number of surgical procedures being performed, problems associated with adhesions are likely to increase. Adopting adhesion prevention strategies will help to address these problems. Clearly, certain procedures have a higher risk of causing adhesion-related readmission. Particular precaution should be taken in these 'high-risk' procedures.

The last consensus to be reached regarding adhesion formation and prevention was in 1997.[8] It recognised the need for good surgical practice and appropriate use of new anti-adhesion adjuvants Despite these recommendations, the burden of adhesions remains. Interestingly, in a questionnaire study among Swedish obstetricians and gynaecologists, 40% of those questioned had never used any method of adhesion prevention.[29] In addition, there was generally a lack of interest and awareness of adhesion prevention strategies as well as large differences in surgical technique

Since the 1997 consensus on adhesion prevention and treatment much has happened. The SCAR study and, most recently, the SCAR-2 epidemiological studies, have provided comprehensive data on the incidence of adhesion-related readmissions following lower abdominal or pelvic surgery. In addition, new and more effective anti-adhesion products are now becoming available. This coupled with a greater emphasis on quality and risk management issues has re-focused attention on adhesion prevention strategies.

Approaches to adhesion prevention

A range of adhesion prevention strategies and techniques were reviewed by Risberg 1997.[28] Two major prevention strategies were identified: good surgical technique and the application of anti-adhesion adjuvants.

Good surgical technique

Good surgical technique has been recognised as being particularly important for adhesion prevention. This should include:

- gentle tissue handling (minimal use of forceps, retractors and clamps on tissue not intended for removal)
- meticulous haemostasis (avoid blood in the peritoneum)
- irrigation to minimise serosal drying
- avoiding intraperitoneal infection
- minimising foreign bodies such as glove powder

Table 1. Adhesion reduction agents

Agent	Materials	Availability
Site-specific		
Preclude®	Expanded polytetrafluoroethylene Gore-tex® sheet	Generally unavailable
Interceed®	Oxidised regenerated cellulose fabric	
Seprafilm®	Hyaluronic acid carboxymethylcellulose film	
SprayGel™	Polyethylene glycol hydrogel	
Surgiwrap™	Copolymer 70:30 poly(L-lactide-co-D, L-lactide) sheet	
Broad		
Hyskon®	32% dextran 70 solution	Generally unavailable
Sepracoat®	0.04% hyaluronic acid-phosphate-buffered saline	Withdrawn
Intergel®	0.5% ferric hyaluronate gel	Withdrawn
Adept®	Icodextrin 4% solution	

- the use of fine nonreactive sutures
- taking care during cauterisation to prevent ischaemia.

Anti-adhesion adjuvant solutions/drugs

Several adjuvant solutions and drugs have been used to prevent adhesions including nonsteroidal anti-inflammatory drugs (NSAIDS), corticosteroids and fibrinolytics.[25] NSAIDs (e.g. ibuprofen, tolmetin, oxyphenbutazone) have been widely studied and can be administered systemically as well as intraperitoneally. The clinical efficacy of NSAIDS, however, is questionable.[25] Corticosteroids show poor efficacy and are associated with immunosuppression and delayed wound healing, such as infection, incisional hernia and wound dehiscence. Furthermore, corticosteroids do not remain in the peritoneal cavity for the duration of adhesion formation (four to five days post-surgery). Fibrinolytics are also used but there is a risk of impaired wound healing and/or bleeding by preventing or reversing fibrin deposition. Intraperitoneal or systemic tissue plasminogen activator (tPA), streptokinase and elastase have all undergone extensive clinical evaluation with conflicting results.[25] In some cases fibrinolytics have been associated with haemorrhagic complications. Their lack of efficacy may be attributed to rapid peritoneal absorption and clearance.

Clearly, these agents are far from ideal. To assess opinion on postoperative adhesions, two surveys were conducted at the European Society of Human Reproduction and Embryology (ESHRE 2002) and the European Association of Coloproctology (EACP 2002). According to respondents, four main attributes are associated with an ideal anti-adhesion agent. A potential agent should be safe, efficacious (at the operation site and throughout the cavity), easy to use in all types of abdominal surgery (open and laparoscopic) and economical.[29]

Adhesion-reducing agents generally fall within two main categories:

- physical barriers, e.g. Preclude®, Interceed®, Seprafilm®, SprayGel™, Surgiwrap™
- solutions, e.g. crystalloid solutions including Ringer-Lactate/saline with or without heparin, Hyskon®, Intergel®, Sepracoat®, Adept® (Table 1).

Generally, the physical barriers tend to be site specific, whereas solutions have the advantage of providing broad coverage throughout the cavity.

Many of these agents, however, do not meet the four requirements for the ideal anti-adhesion agent. There are toxicity concerns with Hyskon® and Intergel®. While Hyskon® has been used it was not approved as an anti-adhesion agent; Intergel® was withdrawn in 2003. Preclude® and Seprafilm® are not easy to handle. Preclude® has to be sutured in place and should then be removed at a later date; it is rarely if ever used nowadays. It is difficult to use Seprafilm® laparoscopically and Interceed® is rendered ineffective in the presence of blood. SprayGel™ requires specialist equipment and technique to use and is under study. Surgiwrap™ is also under study. The physical barrier agents, while reducing adhesions where they are placed, have no effect on the development of adhesions throughout the pelvic cavity. The most widely used agents

Table 2. Clinical development status of adhesion reduction agents

Agent	Approved (Europe)	Safety profile	Limitations	Clinical studies[a]	Cost
Site-specific					
Preclude®	Yes	Yes	Suture in place	2	£££
Interceed®	Yes	Yes	Blood incompatibility	24+	£
Seprafilm®	Yes	Anastomosis?	Handling	4+	£££
SprayGel™	Yes	?	Complex and capital equipment	2[b]	£££
Surgiwrap™	Yes	No	Suture in place but dissolves in one year	0	£££
Broad					
Hyskon®	No	Anaphylaxis	Toxicity	3	£
Sepracoat®	Withdrawn: FDA did not approve – poor efficacy				
Intergel®	Withdrawn: late-onset postoperative pain				
Adept®	Yes	38 000 patient-years 7.5% solution	Main studies continuing	4	£

[a] Continuing and complete; [b] Pivotal trail stopped owing to poor efficacy

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

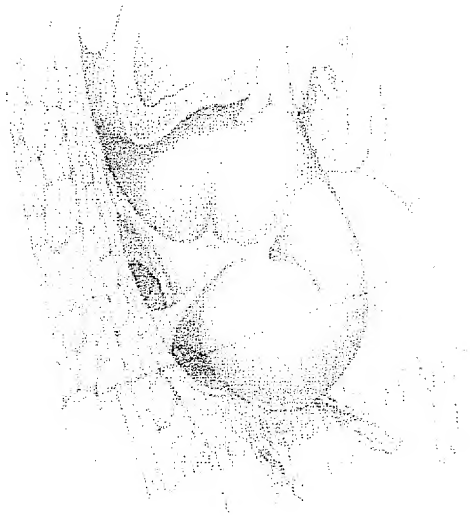
For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 6

Togas Tulandi, MD, MHCM
Professor of Obstetrics and Gynecology. Milton Leong Chair in Reproductive Medicine. McGill University. Montreal, Quebec

Mohammed Al-Sunaidi, MD
Fellow in Reproductive Endocrinology and Infertility. McGill University. Montreal, Quebec

The authors report no financial relationships relevant to this article.



Adhesions that form between the small bowel and abdominal wall can cause severe constrictions that obstruct the bowel

Averting adhesions: Surgical techniques and tools

A laparoscopic approach, microsurgical principles, and barriers or instillates can reduce adhesions

CASE: Could bowel obstruction have been prevented?

B.H., 34, undergoes laparotomy for removal of an 8-cm myoma and a left ovarian cyst, which is found to be an endometrioma. Now she has come to the emergency department complaining of abdominal distension, pain, vomiting, and an inability to defecate. Small-bowel obstruction is diagnosed. Another laparotomy reveals that the obstructed bowel is adhered to the prior surgical incision.

Could this scenario have been avoided?

Adhesions need no introduction. Every surgeon is familiar with them; they are so ubiquitous they sometimes seem to be a given. Nevertheless, there are steps you can take to reduce the incidence of postoperative adhesions. In this article we describe surgical techniques, barriers, and peritoneal instillates that can help.

Why worry?

Intra-abdominal adhesions can cause pain, infertility, and bowel obstruction, and complicate future surgeries.[1-3] Most studies suggest that more than 50% of women with adhesion-related small bowel obstruction have a history of gynecologic or obstetric operations. Within 1 year of laparotomy, adhesions cause intestinal obstruction in 1% of patients. After even a single previous abdominal operation, 93% of patients develop

adhesions, compared with only 10.4% of patients who have never undergone laparotomy (FIGURE 1, page 91).[1-3]

We recently found an incidence of adhesion-related intestinal obstruction after operation for a benign gynecologic indication of 8 cases per 1,000 operations.[4] Total abdominal hysterectomy (TAH) was the most common cause of small bowel obstruction (13.6 cases per 1,000 surgeries).

Surgical technique

Basic strategies

Tissue desiccation, necrosis, and the use of reactive suture material can predispose the patient to adhesion formation. Many studies in animal models have demonstrated an association between adhesions and these parameters. The following practices can help:

- Continuously irrigate the operative field during laparotomy
- Use nonreactive suture material such as polyglycolic acid (Dexon), polyglactin (Vicryl), or polydioxanone (PDS). Using reactive material, such as catgut, is discouraged
- Use powder-free gloves and prevent foreign-body infiltration (eg, powder, gauze, lint) of the wound.

No single parameter is as important as good surgical technique, attention to microsurgical principles, and precise hemostasis (TABLE 1).

Peritoneal closure is unnecessary

Several randomized trials have demonstrated that closure of the parietal or visceral peritoneum is unnecessary. This practice is associated with slightly longer operating times and greater postoperative pain and may cause more adhesions.[5] In 1 study, the rate of adhesion formation after laparotomy with peritoneal closure was 22.2%, compared with 16% without closure.[6]

Ellis[7] noted an increasing number of medicolegal claims arising from adhesion-related complications, and recommended that "peritoneal defects and the pelvic floor should be left open, since they rapidly reperitonealized."

Surgical principles to reduce adhesion formation

Take a laparoscopic approach when feasible

Minimize tissue necrosis

Provide meticulous hemostasis

Liberally irrigate the abdominal cavity

Use nonreactive suture materials

When performing laparotomy
- Avoid contamination with glove powder, lint, or other foreign bodies
- Do not suture the peritoneum

Laparoscopy is more protective than open surgery

Abdominal surgeries injure tissues more severely than laparoscopy, and are associated with a greater degree of adhesion formation in up to 94% of patients, although laparoscopy can also cause adhesions.[2] Laparoscopy is more protective because it involves minimal handling of tissue and little manipulation of the internal organs. Surgery is performed in a closed environment, tissue moistness is maintained, and contamination with glove powders or lint does not occur. In addition, the tamponade effect of carbon dioxide pneumoperitoneum facilitates hemostasis. Laparoscopy is also associated with a lower incidence of infection.

FAST TRACK

To reduce the likelihood of adhesions, do not suture the peritoneum after abdominal operations

Adhesion-reducing substances

Many adhesion-reducing products have been evaluated in human and animal models. A basic assumption behind these substances is that surgically injured tissues heal without forming adhesions if the traumatized surfaces in apposition are separated to allow each to heal independently.

CONTINUED

The array of selected adhesion barriers and peritoneal instillates, and how they work

PRODUCT	SPECIAL FEATURES
Barriers	
Expanded polytetrafluoroethylene (Preclude [Gore-Tex surgical membrane])	• Very effective • Nonreactive • Nondegradable • Requires fixation to the tissue • Difficult to apply by laparoscopy • Unpopular
Hyaluronic acid and carboxymethylcellulose (Seprafilm)	• Blood-insensitive • Brittle and sticky • Difficult to use by laparoscopy
Oxidized regenerated cellulose (Interceed [TC7])	• The most widely studied material • Easy to handle • Blood-sensitive
Instillates	
4% icodextrin (Adept)	• Requires high volume (1 L) • Decreases adhesion formation and reformation after laparoscopic gynecologic surgery
Hyaluronic acid and ferric ion (InterGel)	• Effective • Withdrawn from market
HAL-C bioresorbable membrane (Sepracoat)	• Absorbed within 7 days • Reduces tissue desiccation
Hydrogel (SprayGel) to form membrane	• Two polymers must be combined • Sprayable • Easy to use at laparoscopy • Pivotal study stopped prior to completion
Hydrogel (Adhibit)	• Not available in the US
Fibrin sealant (Tissucol)	• Scarce data

The ideal substance is resorbable, adherent to the traumatized surface, applicable through the laparoscope, and inexpensive, with high biocompatibility. So far, no substance or material has proved to be unequivocally effective.

Adhesion barriers are widely studied

The following products are among the most widely investigated substances (TABLE 2).

Expanded polytetrafluoroethylene, or ePTFE. Gore-Tex surgical membrane, constructed of ePTFE (Preclude, WL Gore), is nonabsorbable and produced in thin sheets (0.1 mm), with an average pore size of less than 1 µm. It is sutured to the tissue so that it overlaps the incision by at least 1 cm. It prevents adhesion formation—and reformation—independent of the type of injury. It is also effective in the presence of blood.

In a randomized trial, ePTFE decreased postmyomectomy and pelvic sidewall adhesions.[8,9] In our experience, this is the most effective adhesion-reducing substance available. It is not widely used, however, because it is nonabsorbable and has to be fixed to the tissue.

Combined hyaluronic acid (HA) and carboxymethylcellulose (CMC). Known most widely by its trade name, Seprafilm (Genzyme Corp), this bioresorbable product is composed of sodium HA and CMC, a combination that produces a transparent and absorbable membrane that lasts for 7 days after application.[10,11]

In a study of 259 patients undergoing laparotomy for bowel resection or enterolysis, the incidence of repeat bowel obstruction was similar in the group treated with Seprafilm and the historical control group.[1] However, 9 of 12 bowel obstructions in the treated group resolved without surgery, compared with 5 of 12 in the control group. The enterolysis rate in the treated group was 1.5%, compared with 3.9% in the control group.

Because of its stickiness, Seprafilm is not ideal for laparoscopy. However, it can be rolled and passed through the trocar, with the film separated from its paper backing inside the abdominal cavity.

Oxidized regenerated cellulose. Known under the brand name Interceed (TC7), this absorbable adhesion barrier (Johnson & Johnson) is the most widely studied product available today. Several randomized trials have shown that it reduces postoperative formation of adhesions on the pelvic sidewalls and near the adnexa.[12–14]

CONTINUED

The efficacy of Interceed is reduced in the presence of blood. It is the easiest adhesion barrier to use at laparoscopy.

Newer agents in development include CMC and polyethylene oxide (PEO) composite gel (Oxiplex/AP, FrizoMed) and polylactide (PLa): copolymer of 70:30 Poly (L-lactide-co-D,L-lactide) film (SurgiWrap, Mast Biosurgery)

Peritoneal instillates

The newest peritoneal instillate is 4% icodextrin solution (Adept, Baxter BioSurgery). It is FDA-approved for the reduction of adhesion reformation after laparoscopic adhesiolysis. In a randomized study, the authors found that instillation of 4% icodextrin solution decreased adhesion formation and reformation after laparoscopic gynecologic surgery.[15]

Hyaluronic acid. Intergel (Lifecore, Johnson & Johnson Gynecare) is a cross-linked HA with ferric ion. It effectively reduces the number, severity, and extent of adhesions after abdominal operation.[16] However, the product was withdrawn from the market after several reports of late-onset postoperative pain requiring surgery.

Sepracoat. This product (HAL-C Bioresorbable Membrane, Genzyme Corp) is a modification of Seprafilm. It coats serosal surfaces and is absorbed from the peritoneal cavity within 7 days. Its mechanism of action includes the reduction of tissue desiccation. Preliminary data show it to be effective in reducing postoperative adhesions.[17] However, it did not receive FDA approval for clinical use, and was withdrawn from the market in 1997.

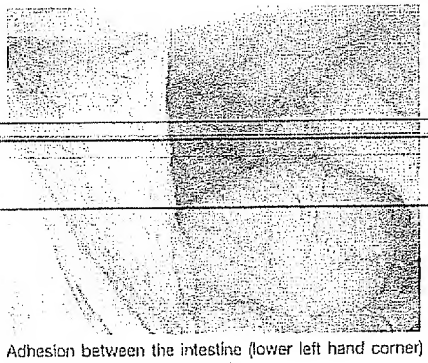
Hydrogel. A novel technique of substance delivery into the abdominal cavity is by combining 2 streams of liquid polymers, delivered via catheter to target tissue. When combined, the 2 streams produce a solid polymer within minutes. Sprayable hydrogel (SprayGel, Confluent Surgical) can be easily applied at laparoscopy. The solid polymer acts as an adhesion barrier and can potentially serve as a vehicle for localized delivery of drugs.

In a randomized study, Mettler et al[18] evaluated 66 women who underwent myomectomy with or without SprayGel application. Second-look laparoscopy was performed in 40 women. Seven of 22 patients (31.8%) in the SprayGel

Adhesions through the laparoscope

Severe adhesions between the intestines and omentum to the uterus.

Omental adhesions to the anterior abdominal wall



Adhesion between the intestine (lower left hand corner) and the anterior abdominal wall

FAST TRACK

A novel technique is to combine 2 streams of liquid polymer via catheter to produce a solid polymer over the target tissue

group and 2 of 18 patients (11.1%) in the control group remained free of adhesions. However, the power of this study is small, and the authors did not break the women into subgroups based on whether they underwent surgery via laparoscopy or laparotomy. In the United States, the pivotal study of SprayGel was stopped prior to completion.

A similar product is a sprayable self-polymerizing gel called Adhibit (Angiotech). An unpublished study from Europe showed it to be promising.

Fibrin sealant. Fibrin glue (Tissucol, Baxter) has been used as an adhesion-reducing substance, although clinical data on this application are scarce. This product is not approved by the FDA.

Which operations are the biggest culprits?

Myomectomy

Myomectomy performed through a laparotomy incision usually causes adhesions, so women who undergo this operation are good candidates for adhesion-reducing substances. The rate of adhesion formation after abdominal myomectomy is more than 90%—and it is 70% by laparoscopy.

Two helpful preventive strategies:

- Use a laparoscopic approach when feasible, and
- apply a barrier, such as the Gore-Tex ePTFE membrane, Seprafilm, or, if the myomectomy incision is not oozing, Interceed. Instillation of 1 L of 4% icodextrin may also be useful.

Hysterectomy

Most small-bowel obstruction follows abdominal hysterectomy, although a considerable period of time may pass before the problem occurs. When it does, a general surgeon usually manages the patient, and the treating gynecologist is unaware of this serious complication.

We recently found an incidence of adhesion-related small-bowel obstruction of 14 cases per 1,000 total abdominal hysterectomies and 1 case per 1,000 vaginal hysterectomies ($P<.001$).[4] We did not encounter any small-bowel obstruction among 303 cases of laparoscopic supracervical hysterectomy.

Application of an adhesion-reducing substance to the vaginal vault or cervical stump may prevent small-bowel obstruction. Most adhesions implicated in small-bowel obstruction involve the vaginal vault. Appropriate products include Interceed, Preclude, Seprafilm, or perhaps Adept.

Fertility-promoting surgery

No adhesion-reducing substance has proved to be effective in increasing the pregnancy rate after a fertility-promoting procedure such as reconstructive tubal surgery or surgery for endometriosis.

FAST TRACK

No adhesion-reducing substance can improve the pregnancy rate after fertility-promoting surgery

CASE Recommendations

B.H., the patient described at the beginning of this article, should have had her initial surgery performed by an experienced laparoscopist, with minimal coagulation, meticulous hemostasis, "layered" repair of the myomectomy incision using nonreactive sutures, and liberal irrigation of the abdominal cavity. At the conclusion of the operation, the incision could have been covered with Gore-Tex surgical membrane or Seprafilm (or Interceed if there was no oozing) at least 1 cm beyond the incision. Instillation of Adept might have been useful as well.

The second operation also should have involved a laparoscopic route, which is associated with a lower rate of adhesions and could have reduced her risk of further bowel obstruction. ■

References

1. Diamond MP. Incidence of postsurgical adhesions. In: diZerega G, ed. Peritoneal Surgery. New York: Springer-Verlag; 2000:217–223.
2. Tulandi T, Al-Shahrani A. Adhesion prevention in gynecologic surgery. Curr Opin Obstet Gynecol. 2005;17:395–398.
3. Al-Took S, Platt R, Tulandi T. Adhesion-related small bowel obstruction after gynecologic operations. Am J Obstet Gynecol. 1999;180:313–315.

CONTINUED

4 Al-Sunaidi M, Tulandi T. Adhesion-related bowel obstruction after hysterectomy for benign conditions. Obstet Gynecol. 2006;108:1162–1166.

5 Tulandi T, Al-Jaroudi D. Non-closure of peritoneum: a reappraisal. Am J Obstet Gynecol. 2003;189:609–612.

6 Tulandi T, Hum HS, Gelfand MM. Closure of laparotomy incisions with or without peritoneal suturing and second-look laparoscopy. Am J Obstet Gynecol. 1988;158:536–537.

7 Ellis H. Medicolegal consequences of postoperative intra-abdominal adhesions. J R Soc Med. 2001;94:331–332.

8 Franklin R, Haney A, Kettel L, et al. An expanded polytetrafluoroethylene barrier (Gore-Tex surgical membrane) reduces post-myomectomy adhesion formation. Myomectomy Adhesion Multicenter Study Group. Fertil Steril. 1995;63:491–493.

9 Haney A, Hesla J, Hurst B, et al. Expanded polytetrafluororethylene (Gore-Tex surgical membrane) is superior to oxidized regenerated cellulose (Interceed TC7) in preventing adhesions. Fertil Steril. 1995;63:1021–1026.

10 Diamond MP, and the Seprafilm Adhesion Study Group. Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. Fertil Steril. 1996;66:904–910.

11 Vrijland WW, Tseng LN, Eijkman HJ, et al. Fewer intraperitoneal adhesions with use of hyaluronic acid–carboxymethylcellulose membrane: a randomized clinical trial. Ann Surg. 2002;235:193–199.

12 Sekiba K. The use of Interceed (TC7) absorbable adhesion barrier to reduce postoperative adhesion reformation in infertility and endometriosis surgery. Obstetrics and Gynecology Adhesion Prevention Committee. Obstet Gynecol. 1992;79:518–522.

13 Azziz R, and the Interceed (TC7) Adhesion Barrier Study Group II. Microsurgery alone or with Interceed absorbable adhesion barrier for pelvic side wall adhesion reformation. Surg Gynecol Obstet. 1993;77:135–139.

14 Nordic Adhesion Prevention Study Group. The efficacy of Interceed (TC7) for prevention of reformation of postoperative adhesions on ovaries, fallopian tubes, and fimbriae in microsurgical operations for fertility: a multicenter study. Fertil Steril. 1995;63:709–714.

15 DiZerega GS, Verco SJ, Young P, et al. A randomized, controlled pilot study of the safety and efficacy of 4% icodextrin solution in the reduction of adhesions following laparoscopic gynaecological surgery. Human Reprod. 2002;17:1031–1038.

16 Hill-West JL, Dunn RC, Hubbell JA. Local release of fibrinolytic agents for adhesion prevention. J Surg Res. 1995;59:759–763.

17 Diamond MP. Reduction of de novo postsurgical adhesions by intraoperative precoating with Sepracoat (HAL-C) solution: a prospective, randomized, blinded, placebo-controlled multicenter study. The Sepracoat Adhesion Study Group. Fertil Steril. 1998;69:1067–1074.

18 Mettler L, Audebert A, Lehmann-Willenbrock E, Schive-Peterhansl K, Jacobs VR. A randomized, prospective, controlled, multicenter clinical trial of a sprayable, site-specific adhesion barrier system in patients undergoing myomectomy. Fertil Steril. 2004;82:398–404.

rely solely on this mobility to determine whether or not a trial of forceps or vacuum is indicated. Because the basovertical diameter of the fetal head can be elongated, it is possible to palpate the leading edge of the skull below the ischial spines and still have an unengaged fetal head. This is exactly the circumstance in which a vaginal examination will give false reassurance of the chance of success. In this circumstance, although part of the skull is below the plane of the ischial spines, the widest diameter of the fetal head (usually the biparietal diameter) is still above the plane of the maternal pelvic brim, and the fetal head is unengaged.

I would argue against moving ahead with a "trial of forceps in the OR" in cases with a "tight fit." As discussed in the article, significant molding implies stretching of the underlying soft tissue. In my opinion, proceeding with an operative vaginal delivery in the case of a fetus with 3+ molding would be riskier than is justified. Operative vaginal delivery should be offered only when it is almost certain to succeed. For that reason, I would also caution against using a trial of forceps in cases where the outcome is uncertain. Cesarean section may be the safest option in such cases.

I agree completely that liberal use of ultrasound to determine head position and station (if possible) should be encouraged.

I recommend that any forceps delivery that is anything other than an outlet delivery take place in the operating room. In addition, I recommend always having neonatal and anesthesia backup readily available with any operative vaginal delivery attempt unless it is an emergency.

Finally, I agree that the correct application of the forceps is essential. In fact, the most important part of the forceps procedure is what happens before the actual application of traction! If the correct indications have been followed, the patient has been properly assessed and prepared for the procedure, and if all ancillary services are available, the traction effort is usually the least stressful part of the delivery, since it is bound to succeed. ■

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 7

Gynecol Surg (2007) 4:243–253
DOI 10.1007/s10397-007-0333-2

REVIEW ARTICLE

Postoperative abdominal adhesions and their prevention in gynaecological surgery. Expert consensus position. Part 2—steps to reduce adhesions

Rudy Leon DeWilde · Geoffrey Trew ·
On behalf of the Expert Adhesions Working Party
of the European Society of Gynaecological
Endoscopy (ESGE)

Received: 12 July 2007 / Accepted: 12 July 2007 / Published online: 10 August 2007

Abstract This consensus position represents the collective views of 35 gynaecologists with a recognised interest in adhesions. The first part of the position was presented in the previous issue of Gynecological Surgery and reviewed the published literature on the extent of the problem of adhesions. In this part, the opportunities to reduce their incidence are considered. Collective proposals on the actions that European gynaecologists should take to avoid causing adhesions are provided. Importantly, in this part, the need to now inform patients of the risks associated with adhesion-related complications during the consent process is discussed. With evidence increasing to support the efficacy of adhesion-reduction agents to complement good surgical practice, all surgeons should act now to reduce adhesions and fulfil their duty of care to patients.

Keywords Adhesions · Adhesiolysis · Guidelines · Gynaecology · Surgery

R. L. DeWilde (✉)
Department OBGYN, Pius-Hospital,
Oldenburg, Germany
e-mail: rudy-leon.dewilde@pius-hospital.de

G. Trew
Reproductive Medicine and Surgery,
Hammersmith and Queen Charlotte's Hospital,
London, UK
e-mail: g.trew@ic.ac.uk

G. Trew
Imperial College, University of London,
London, UK

Introduction

Adhesions are the most frequent complication of abdominal surgery and may represent one of the greatest unresolved medical problems in medicine today [1], yet, many surgeons are still not aware of the extent of the problem and its serious consequences.

Recent epidemiological data have demonstrated that, despite advances in surgical techniques in recent years, the burden of adhesion-related complications has not changed [2, 3]. While laparoscopic procedures are commonly believed to be less adhesiogenic and cause fewer de novo adhesions to form compared to open surgery [4, 5], for many procedures, the comparative risk of adhesion-related complications following open and laparoscopic gynaecological surgery is similar [3].

Developments in adhesion-reduction strategies and new agents do, however, now offer a realistic possibility of reducing the risk of adhesions forming and, thus, may improve the outcomes for patients and the associated onward burden. The importance of providing clear recommendations on adhesions and their prevention following gynaecological surgery is very apparent.

The paper details the second part of the project undertaken by the Expert Adhesions Working Party of the European Society of Gynaecological Endoscopy (ESGE).

The first paper published in the previous issue of Gynecological Surgery provided an overview of the published literature on the extent of the problem of adhesions and, in this paper, the opportunities to reduce it are presented. A consensus of opinion on the actions that European gynaecologists should now take is provided. These proposals are collective opinions and should not be used for performance measures or competency purposes

Together, these two papers provide a collective consensus position which it is hoped will raise the level of awareness and the understanding of adhesions, and the associated healthcare burden and costs, thereby, encouraging heightened discussions and actions to address this area of unmet need.

Steps to reduce adhesions

The generally accepted method of reducing adhesions is a meticulous surgical technique [6] and, within that, the rules of microsurgery are fundamental [7]. In particular, they need to be re-emphasised in laparoscopic surgery and in the treatment of endometriosis, where there is heightened inflammatory response and angiogenesis, with a corresponding propensity for adhesion development [7] (Table 1).

Many of the traumas that cause adhesions are a routine part of surgery and, even if adhesion-reduction strategies are adopted, there can be conflicts—meticulous haemostasis is very important but, to achieve this, limiting the use of cautery may be problematic. Therefore, even if meticulous and careful surgical technique is employed, postoperative adhesions are very common [8]. Any type of surgery (however experienced the surgeon) at any site can cause postoperative adhesions and, while surgeons should adopt the adhesion reduction steps as listed in Table 1 during all operations, these steps may not be sufficient to prevent adhesion formation, as evidenced by the SCAR study data [2, 3].

Importantly, while surgical adhesiolysis is the current method of managing adhesions, regardless of the method of adhesiolysis or the type of adhesion, it results in further traumatic disruption and a high rate of adhesion reformation (mean 85%), as well as the development of de novo adhesions [9]. Studies indicate that, compared with unaffected peritoneal tissue, adhesive tissue contains higher levels of growth factors, suggesting a greater propensity for adhesion reformation. These factors (fibroblast growth factor) depress fibrinolytic activity and induce tissue fibrosis and, thus, reformed adhesions tend to be more dense and severe than de novo adhesions [10, 11].

Table 1 Adhesion-reduction steps

Carefully handle tissue with field enhancement (magnification) techniques
Focus on planned surgery and, if any secondary pathology is identified, question the risk benefit of surgical treatment before proceeding
Perform diligent haemostasis but ensure diligent use of cautery
Reduce cautery time and frequency and aspirate aerosolised tissue following cautery
Excise tissue—reduce fulguration
Reduce duration of surgery
Reduce pressure and duration of pneumoperitoneum in laparoscopic surgery
Reduce risk of infection
Reduce drying of tissues (limit heat and light)
Use frequent irrigation and aspiration in laparoscopic and laparotomic surgery
Limit use of sutures and choose fine non-reactive sutures
Avoid foreign bodies—such as materials with loose fibres
Minimal use of dry towels or sponges in laparotomy
Use starch- and latex-free gloves in laparotomy

Adhesion-reduction agents

A number of adjuvants and strategies have been investigated, including both pharmacological agents and physical barriers. Decisions on which agent to use are made by the individual surgeon but there is a clear place for agents that are safe, simple to use, clinically effective and affordable.

The quality of research on the use of adhesion-reduction agents is, unfortunately, variable. Most studies have looked at reduction in adhesions as the endpoint. In the majority of cases, the studies have compared the use of an agent with no treatment, sometimes in the same patient. Few studies have been blinded, with most evaluations of adhesion reduction made by the operating surgeon. The variation in adhesion classifications, mode of application of agents, lack of uniformity in surgical approaches and variations in the interpretation of results all make the assessment of the efficacy of the many agents difficult and almost impossible to compare. There are very few studies that have looked at the impact of an agent on clinical outcomes, such as pregnancy, reduction in SBO or ease of reoperative surgery. This is largely because of the complexity of undertaking clinical outcome studies in surgery [12]. Looking at pregnancy as an outcome in women with infertility, which is multi-factorial, is problematic. Likewise, the number of patients needed to power a study to show a reduction in SBO is considerable [12], requiring many centres or a lengthy time period to undertake such work, which can lead to bias with inter-centre and inter-surgeon variables and changes in surgical practice [13]. To date, studies required for regulatory approvals of adhesion-reduction agents have focussed on adhesion reduction [14].

Pharmacological agents

The processes of adhesion formation present various theoretical opportunities for pharmacological intervention. A number of agents have been investigated, including antibiotics, NSAIDs, corticosteroids and fibrinolytics [15, 16]. To date, no clinical studies have shown adhesion-reduction benefits using pharmacological regimens [17] and there are safety concerns with some agents [18, 19]. Theoretically, drugs may be limited by their inability to

reach the site and to stay there long enough to be effective [19], since surgical sites are often poorly vascularised, as are most injury sites. Rapid resorption through the peritoneal membrane occurs with small molecules, thus, removing many agents delivered intraperitoneally. Moreover, many processes involved in adhesion formation are also part of normal wound healing, so any pharmacological agent needs to reduce fibrin deposition, yet still allow for re-epithelialisation.

Research continues on a range of pharmacological agents but they are still at an experimental stage and the practical use of such agents in routine surgery is some way off.

Physical separators

Barriers are currently the only available adjuncts to reduce adhesion formation. The key requirement of any barrier is that it should effectively separate traumatised peritoneal surfaces during the critical period of adhesion development in the 3–5 days after surgery, during which, peritoneal healing occurs [20].

This separation can broadly be achieved by use of site-specific mechanical barriers (films and gels) or by the use of broad-coverage fluid agents to keep tissue surfaces physically separated during the healing process.

The available agents are summarised in Table 2 and outlined in the following sections.

Site-specific mechanical barriers

These have been used for some time, initially in the form of omental or peritoneal grafting. More recently, inert barriers have been introduced to be used at the site of trauma; for example, over a suture line for procedures such as myomectomy.

Table 2 Overview of the available anti-adhesion agents

Agent	Approval		Safety	Limitations	Clinical studies	Cost
	Europe*	US FDA				
Site-specific						
Preclude	✓	✓ Tissue separation	✓	Suture in place	Limited	€€
Interceed	✓	✓ Open	✓	Incompatible with blood Remove irrigants before use Handling	Many studies - One limited pregnancy outcomes study	€€
Seprafilm	✓	✓ Open	✓ But anastomosis	Remove irrigants before use Handling Difficult to apply in laparoscopy	A number of studies - Laparotomy only - SBO study - limited results	€€(€)
SprayGel	✓	No	?	Complex and capital equipment needed	Very limited - Pivotal study halted	€€€
Hyalobarrier gel	✓	No	✓	Handling No irrigation after application	Limited - One limited pregnancy outcomes study	€(€)
SurgiWrap	✓	No	?	Peritoneal replacement film No clinical data on adhesion reduction Suture in place	None	€€(€)
Oxiplex AP gel	✓	No	✓	Availability	Very limited - Pilot studies only	??
Broad coverage						
Adept	✓	✓ Lap	✓	Clinical studies in laparoscopy only	Limited - Double blind study - Active control	€

* At least one country

Preclude® (Gore-tex—expanded polytetrafluoroethylene, PTFE)

One of the first physical membranes used was Preclude®. It has to be sutured in place and is not resorbable, so it has to be removed at a second laparoscopy, which substantially limits its applicability in peritoneal surgery. Preclude® is rarely used in Europe and resorbable barriers have subsequently been introduced which have greater clinical utility.

Interceed® (oxidised regenerated cellulose)

The first resorbable membrane was Interceed®, first introduced in 1990. It forms a viscous gel when it comes into contact with fluids and is completely resorbed after 4 weeks. It can be used at most intraperitoneal locations and in laparoscopic as well as open surgery—although laparoscopic application is challenging [21]. Meticulous haemostasis is important, as the efficacy of the product is reduced in the presence of blood [22, 23]. There is substantial literature on the use of Interceed® in gynaecological surgery and the product has been shown to reduce adhesion formation without affecting wound healing [24–31]. However, the quality of many of the studies is limited by study design, with surgery only as the control. Although a systematic review of the literature in 1999 concluded that no study reported pregnancy or the reduction of pain as an outcome [25], more recent work with Interceed® indicated that its effect on reducing adhesions results in improved pregnancy outcomes in infertile patients [29]. While the number of patients in this study was limited, the use of Interceed® resulted in a significant increase in the pregnancy rate compared to surgical controls. These results are very important for all anti-adhesion agents, as they show that adhesion reduction using an anti-adhesion agent is a valid endpoint.

Seprafilm® (hyaluronic acid/carboxymethylcellulose)

Seprafilm® is another barrier film [32, 33], which is usually placed over a suture line. It persists during the period of re-epithelialisation and is absorbed spontaneously. Seprafilm® does not conform to the shape of the pelvic organs as well as Interceed® and is usually used as a barrier placed between the bowel or omentum and the anterior abdominal wall at the time of wound closure, where it can prevent adherence and, potentially, reduce the risk of enterotomy at subsequent surgery. It is generally difficult to handle and its use in laparoscopic surgery is not realistic. Alongside the main pivotal studies [32, 33], there is mounting literature on its use and it is the only agent to have been investigated for the reduction of SBO [34, 35]. This study reported a significant reduction in adhesive small bowel obstruction requiring reoperation by the use of Seprafilm® (1.6% absolute reduction) [35]. A mean of 4.5 sheets per patient was used to effect adequate coverage, which is costly [34, 35]. While the study also provided confirmation of general safety in colorectal surgery, it highlighted that the use of Seprafilm® at the site of an anastomosis is to be avoided, due to increased anastomotic leaks [34].

SurgiWrap® (polylactide. copolymer of 70 30 Poly [L-lactide-co-D,L- lactide])

SurgiWrap® is a biodegradable polymer film which has a European device licence for the reduction of postoperative adhesions following abdominal, pelvic, gynaecological or cardiac surgery. The supplying company claims that the product has improved handling over alternative film products and a long resorption period of up to 6 months, after which, it is subsequently metabolised to lactic acid, CO_2 and water. The polymer film needs to be sutured in place to prevent it from moving during this period. With the exception of one preclinical study in 44 rats [36], published data are lacking on which to assess the product's safety or its efficacy in reducing peritoneal adhesions. In light of failures of other agents due to long-term safety concerns and in the absence of evidence of clinical efficacy, the use of SurgiWrap® as an adhesion-reduction agent is not to be encouraged at this time.

Gel barriers

A fundamental limitation of site-specific mechanical barriers is the requirement of the surgeon to predict where clinically significant adhesions are likely to form in order to decide where to place the product. In addition, site-specific barriers are difficult to use in laparoscopic surgery. As a result of these limitations, gel barriers have also been developed.

Hyalobarrier® (hyaluronic acid cross-linked to hyaluronic acid)

Hyalobarrier® is a viscous gel, available in Europe as an adhesion-reduction barrier for use after abdominopelvic surgery. It is similar in mode of action to local site-specific film barriers, as it stays at the site to which it is applied, dissolving some days later. There are few published clinical data: there is a small uncontrolled study in myomectomy by laparotomy [37] and two randomised, controlled studies in patients undergoing laparoscopic myomectomy [38, 39]. Although the studies only used limited numbers of patients, they showed a reduction in adhesions and, in the smaller study [38], the pregnancy rate in patients treated with

Hyalobarrier® was significantly greater than in the control group (surgical treatment only) [40] and similar to that seen with Interceed® [29]. Hyalobarrier® is not widely available nor has it been adopted for clinical use in surgery, mainly because it is very sticky and has a tendency to float away from sites when irrigated. These mucoadhesive properties are essential for its efficacy and irrigation is not recommended. However, it has been researched for use in reducing intrauterine adhesions following hysteroscopic surgery with success [41–43] and may be useful in this situation.

SprayGel® (synthetic polyethylene glycol (PEG) solutions)

SprayGel® is a gel barrier coating system which was approved for use in laparoscopic and open surgery in Europe at the end of 2001. It consists of two water-based PEG solutions, one clear and one coloured with methylene blue, to make it easy to see where it has been used. When sprayed together, these two solutions react with each other at the target tissue, where they mix to form a hydrogel film that provides a physical barrier. This barrier remains in place for up to 7 days and is then absorbed and excreted through the kidneys.

In preliminary clinical trials, the use of SprayGel® resulted in a decrease in the incidence, severity and extent of post-surgical adhesion formation [44, 45]. A larger scale pivotal study had commenced in the USA but was then stopped due to lack of efficacy in the treatment compared to the control arm and has not, to date, been resumed.

The use of SprayGel® is limited by the complex setting up of the equipment and the skill and time required to spray and coat tissues evenly. It is also expensive. If there is extensive operative surgery in the pelvis as well as abdominal adhesiolysis, it may be necessary to use two kits and as many as five kits to effect adequate coverage of the complete peritoneal wound area [46].

Oxiplex®/AP (carboxymethylcellulose (CMC) and polyethylene oxide (PEO) composite gel)

Most recently, Oxiplex®/AP, a viscoelastic gel, has been approved for use in Europe as an adhesion-reduction barrier for abdominal/pelvic surgery. It has been used in another formulation for a number of years for the reduction of adhesions in spinal surgery [47]. Two clinical pilot studies in laparoscopic gynaecological surgery comparing use of this gel with no treatment have recently been published [48, 49]. They are primarily safety studies and are, thus, empowered to assess the safety and not the efficacy of the agent. However, in both studies, there was an improvement in the American Fertility Society (AFS) scores compared to the no-treatment controls and the European pilot study demonstrated a significant reduction in adnexal adhesions [48].

These gel agents, like the film barriers, are site-specific, requiring surgeons to predict sites at which adhesions may form and, thus, where the film barrier needs to be applied. However, the pathogenesis of adhesion formation reaches beyond the operative site of actual surgical trauma. The effects of ischaemia, heat, drying, handling and contamination mean that agents providing protection throughout the peritoneal cavity could be advantageous.

Broad-coverage fluid agents

Various broad-coverage agents have been developed but most have been abandoned (Hyskon® [50]) or withdrawn due to safety issues (Intergel® [51]) or the lack of efficacy (Hyskon® [52], Sepracoat®).

Hydroflotation has long been suggested as a technique that may be efficacious, both at the site of application and elsewhere in the pelvis. It involves the instillation of a fluid into the peritoneal cavity at the end of the procedure to provide a physical fluid barrier, preventing the apposition of damaged peritoneal surfaces. Saline, lactated Ringer's solution or Hartmann's solution have all been used widely. However, these crystalloid solutions are absorbed rapidly and do not reduce adhesions [53]. They are absorbed from the peritoneal cavity at the rate of 30–50 ml per hour, so that, by 24 hours after surgery, little, if any, solution is left in the pelvis [54–56]. Studies have also shown that some irrigants, including lactated Ringer's solution, can have deleterious effects on the delicate mesothelial lining of the peritoneum [57, 58].

Adept® (4% icodextrin solution)

Adept® is the single approved and available adhesion-reduction solution that has a sufficiently long intraperitoneal residence [59] to provide coverage throughout the peritoneal cavity and persist through the critical period of adhesion formation [20]. Adept® has been approved in Europe since 2000 as an adhesion-reduction agent in open and laparoscopic gynaecological and general surgery. In the USA, it was recently approved by the FDA for use as an irrigant and post-operative instillate in gynaecological laparoscopy with adhesiolysis. It is the first anti-adhesion agent to be granted such approval. Adept® is a non-viscous, iso-osmotic, clear solution which handles like normal saline, requires no change to surgical practice or any special training. It does not potentiate infection [60] and no differences have been demonstrated between Adept® and lactated Ringer's solution (LRS) in the healing and strength of midline incisions and bowel anastomoses [61].

Early work with Adept® as an anti-adhesion agent showed that it is best used throughout surgery as an irrigant fluid to reduce dessication and following surgery as an instillate (1000 mL) [60, 62]; all work with Adept® has used this combined approach.

Initial clinical studies were encouraging [62] and, recently, efficacy has been further established in a pivotal randomised USA multi-centre study in gynaecological laparoscopy [63]. This study is the largest and the first double-blind study of an anti-adhesion agent. As well as confirming the safety of Adept®, the data demonstrate a significant reduction in adhesions throughout the peritoneal cavity when Adept® is used as an irrigant and post-operative instillate.

A European patient registry (ARIEL) for Adept® use was established alongside the formal clinical trial programme, providing surgeons' feedback on the use and safety of Adept® in routine open and laparoscopic gynaecological [64] and general surgery [65] in 4,620 patients—2,882 of whom underwent gynaecological surgery (2,069 laparoscopy, 813 laparotomy). The study showed that, in routine use, Adept® is well tolerated by patients, is easy to use and has a good safety profile.

Areas of future research

Laparoscopic pneumoperitoneum

While it is widely considered that laparoscopy may be less adhesiogenic than laparotomy, there are some inconsistencies when epidemiological data on adhesion-related outcomes are considered [3]. Since laparoscopy is minimally invasive and, thus, associated with less surgical trauma than laparotomy, there is rising concern that the CO_2 pneumoperitoneum may be an important adhesiogenic factor. This may be due to the CO_2 inducing local changes such as intraperitoneal acidosis [66–68] or, in the absence of moistening, dessication of the mesothelium [69]. The intraperitoneal pressure associated with prolonged pneumoperitoneum may also induce adverse effects on the microcirculation [70, 71], possibly inducing hypoxaemia [72]. This hypoxia, together with other mesothelial insult, may stimulate the expression of factors such as vascular endothelial growth factor (VEGF), resulting in an increase in adhesion formation [72]. As a result of this animal work, active research for other potential adhesion-reduction strategies involving insufflators has begun [73, 74].

Cost-effectiveness of anti-adhesion agents

Post-operative adhesions clearly have an important impact on the successful clinical outcome of surgery and pose an important cost burden. In considering the use of an adhesion-reduction agent, factors to be taken into consideration include not only its safety, ease of use and clinical efficacy, but also whether it is cost-effective. While it is difficult to evaluate the impact that an anti-adhesion agent will have on subsequent clinical outcomes and, thus, whether it will be cost-effective [12], it is possible to model this.

Epidemiological data from the SCAR study [75] have been used to model the cumulative costs over time of adhesion-related hospital readmissions following surgery with or without the use of an adhesion-reduction agent [12] and have recently been updated with the costs of inflation. This model is helpful in understanding the value of different adhesion-reduction agents and suggests that a suitably priced and effective agent can result in overall cost savings to a healthcare system. For example, agents costing around €130 only need to demonstrate a 26% reduction in adhesion-related readmissions 3 years after surgery to return their costs, whereas agents costing around €300 per operation would need to demonstrate at least a 60% reduction in adhesion-related readmissions 3 years after surgery to return the costs of their investment (Fig. 1) [12].

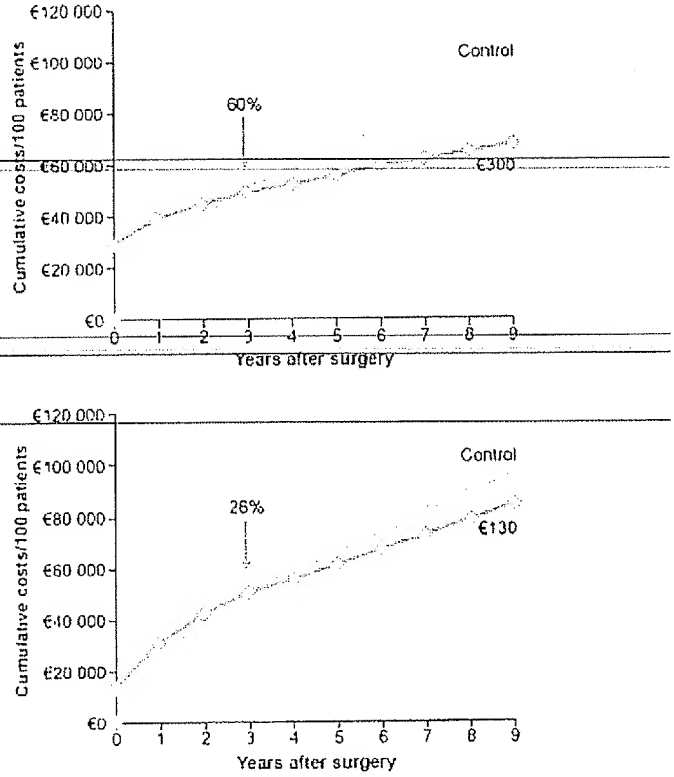


Fig. 1 Cumulative costs of adhesion-related readmissions for 100 patients, following surgery with or without an adhesion-reduction agent. Modelled on the efficacy required to pay back the cost of treatment after 3 years [12] for €130 and €300 agent costs

In either scenario, extension of the model assessment period beyond 3 years after surgery results in cost savings.

It is clear from this that, in considering the choice of an adhesion-reduction agent, the cost as well as the clinical impact of the agent needs to be considered carefully. This is particularly the case if the prophylactic use of adhesion-reduction agents is to be adopted widely in routine surgery.

Advising patients and medicolegal considerations

Even with advances in surgical techniques, it is clear that adhesions remain a common consequence of surgery, with serious health implications for patients, including SBO, infertility and chronic pelvic pain. Even if adhesions are "silent," posing no apparent issues for the patient, the risks of complications at reoperative surgery and late SBO onset are considerable.

Adhesion-related complications are increasingly becoming the subject of forensic and medicolegal debate and there is evidence that medicolegal litigation resulting from complications secondary to postoperative adhesion formation are adding to the healthcare costs and the clinician's burden [76, 77].

In the consent process, it is recommended that patients should be advised of the reasons for and nature of the procedure, the benefits, risks, discomforts and alternatives and the consequences of not undergoing the procedure.

It is common practice in the consent process to advise patients of risks of complications, such as general anaesthesia (<1:100), and general complications after laparoscopic surgery, e.g. pain, bleeding, infection, damage to the bowel/bladder/urethra (1:1000 in sterilisations and 1:500 for other procedures) [78]. These risk ratios are less than the risk of a directly adhesion-related readmission (adhesiolysis) in the first year after surgery following a known high-risk laparoscopic procedure, such as an ovarian or tubal procedure, or open ovarian surgery (1:80 following laparoscopic surgery and 1:50 following open surgery). Even in patients undergoing other therapeutic laparoscopic surgery (excepting tubal sterilisations), the risk of a directly adhesion-related readmission is 1:70 and, for open surgery on the Fallopian tubes or uterus, it is 1:120 and 1:170, respectively, i.e. comparatively high [3].

The International Adhesions Society undertook a survey to review the information on adhesions that patients received [79, 80]. In only 10.4% of cases were adhesions mentioned as part of the informed consent process and in 14.4% adhesions were discussed but were not part of the consent process. In patients undergoing specific adhesiolysis surgery, 54% reported being given some kind of information about adhesions but only 46% were given information on adhesion-reduction agents. In procedures not involving adhesiolysis, only 10% of patients reported receiving any adhesion information and only 6% were given information on adhesion-reduction agents.

Tissue damage to underlying structures during laparoscopic surgery has been shown to be the most common cause of successful surgical negligence suits [81] and it is estimated that the risk of bowel injury is between 10% and 25% of laparoscopic adhesiolysis cases [82] and there is a 19% risk of inadvertent enterotomy during reoperative laparotomy [83]. Furthermore, in a study of misadventure data following laparoscopic surgery, while injury to the common bile duct was the most frequent problem, perforation of the small bowel or colon was the second most common injury and two-thirds of injuries were not noted until after the end of the surgical procedure [84]. Risk of damage was greater when there were difficulties visualising structures—which can be a common issue when operating on a patient with pre-existing adhesions.

With published evidence suggesting that the long-term risk of adhesion-related complications is high in the majority of gynaecological procedures, there is an urgent need for gynaecologists to be cognisant of the potential for medicolegal action [76, 77, 85] if patients are not informed routinely of the risk of adhesions.

Consensus on how to avoid adhesions

To reduce the risk of adhesions, surgeons should actively consider adopting anti-adhesion strategies as described in Table 1, particularly in "high-risk" gynaecological procedures (whether open or laparoscopic), such as ovarian, endometriosis or tubal surgery, myomectomy and adhesiolysis.

New developments in anti-adhesion products and our practical knowledge of using such agents has increased in recent years. Not all agents are difficult or costly to use and there is now promising evidence of efficacy, not only in the reduction of adhesions, but also in subsequent outcomes, such as reduction in SBO or improvement in pregnancy rates in infertile women.

At present, surgeons largely employ good surgical practice to prevent adhesion formation and adhesiolysis to treat adhesions—despite the high reformation rate [9]. Sound epidemiological studies have shown that, even with advances in surgical practice, adhesions continue to represent a significant burden for patients, surgeons and healthcare systems. Evidence is increasing to support the efficacy of adhesion-reduction agents to complement good surgical practice, including agents that are relatively inexpensive and simple to use (Table 2).

It is also time to advise our patients of the risks associated with adhesion-related complications during the

consent process. Failure to inform patients adequately of the risks could, indeed, result in claims of medical negligence.

Further research on the use of adhesion-reduction agents is essential to better understand their impact on clinical outcomes, recognising that such studies are difficult to undertake [12]. Research also needs to continue into the use of more effective adhesion-preventative agents and combinations of strategies and agents. All surgeons should act now to reduce adhesions, thereby, fulfilling their duty of care to patients.

As the results of further studies on adhesions and adhesion-reduction agents become available, the consensus proposals below should be reviewed.

Consensus proposals: actions to reduce adhesions

1. Adhesions need to be recognised as the most frequent complication of abdominal surgery.
2. Surgeons, other healthcare workers, budget holders and policy makers need to increase their awareness and understanding of adhesions and the associated healthcare burden and costs and take active steps to reduce this.
3. Patients need to be informed of the risk of adhesions, given that adhesions are now the most frequent complication of abdominal surgery.
4. Surgeons who do not advise of the risk of adhesions may put themselves at risk of claims for medical negligence.
5. Surgeons have a duty of care to protect patients by providing the best possible standards of care—which should include taking steps to reduce adhesion formation.
6. Surgeons should adopt a routine adhesion-reduction strategy, at least in surgery at high risk for adhesions, such as:
   - Ovarian surgery
   - Endometriosis surgery
   - Tubal surgery
   - Myomectomy
   - Adhesiolysis
7. Good surgical technique is fundamental to any adhesion-reduction strategy—see Table 1.
8. Surgeons should consider the use of adhesion-reduction agents as part of their adhesion-reduction strategy, giving special consideration to agents with data to support safety in routine abdominopelvic surgery and efficacy in reducing adhesions. The practicality and ease of use of agents, as well as the cost of any agent, will influence their acceptability in routine practice.
9. Further research to understand the impact that adhesion-reduction agents have on clinical outcomes will be important.
10. Research towards more effective preventative agents should be encouraged—including the use of combinations of agents to prevent the formation of de novo adhesions, as well as adhesion reformation.
11. Surgeons need to act now to reduce adhesions and fulfil their duty of care to patients.

Acknowledgements The consensus project and manuscript development was facilitated by Corvus Communications Limited under the direction of Rudy DeWilde and Geoffrey Trew. Special thanks go to the work of Alison Crowe, Alastair Knight and Jill Kirkdale in patiently supporting and encouraging all Adhesions Working Party members to actively contribute and feed back on all stages of the project development.

Appendix

Expert Adhesions Working Party of the ESGE

Members of the Expert Adhesions Working Party of the European Society of Gynaecological Endoscopy (ESGE) are listed below alphabetically. All members actively contributed to the development and review of the consensus paper, recognising the importance of publishing on a matter of such importance. The majority participated at the Adhesions Consensus Expert Workshop convened during the 15th Annual Congress of the ESGE and the project was progressed in accordance with accepted processes for the development of consensus statements (see Consensus Process including Conflict of Interest in part 1 published in the previous issue of Gynecological Surgery [86])

Prof. Rudy Leon DeWilde, Pius Hospital, Oldenburg, Germany

Mr Geoffrey Trew, Hammersmith Hospital, London, UK

Dr. Stefano Angioni, H San Giovanni di Dio, Cagliari, Italy

Prof. Alain Audebert, Rue de Turenne, Bordeaux, France

Prof. Pedro Barri, Institut Universitari Dexeus, Barcelona, Spain

Prof. Charles Chapron, Clinique Universitaire Baudelocque, Paris, France

Prof. Maria Elisabetta Coccia, Ospedale di Careggi, Florence, Italy

Prof. Michel Degueldre, Centre Hospitalier Universitaire St-Pierre, Brussels, Belgium

Prof. Gere diZerega, Keck School of Medicine, University of Southern California, Los Angeles, USA

Prof. Enrique Garcia, Instituto Valenciano de Oncologia, Valencia, Spain

Dr Robert J S Hawthorn, Southern General Hospital, Glasgow, Scotland

Dr Petra Janssen, Klinikum Konstanz, Konstanz, Germany

Prof Philippe R Koninckx, University Hospital Gasthuisberg, Leuven, Belgium

Prof. Matthias Korell, Klinikum Duisburg, Wedau Kliniken, Duisburg, Germany

Dr Stefano Landi, Ospedale Sacro Cuore, Verona, Italy

Mr Adrian M Lower, The London Clinic, London, UK

References

1 Diamond MP, El-Hammady E, Wang R, Kruger M, Saed G (2004) Regulation of expression of tissue plasminogen activator and plasminogen activator inhibitor-1 by dichloroacetic acid in human fibroblasts from normal peritoneum and adhesions. Am J Obstet Gynecol 190:926–934

2 Lower AM, Hawthorn RJS, Ellis H, O'Brien F, Buchan S, Crowe AM (2000) The impact of adhesions on hospital readmissions over ten years after 8849 open gynaecological operations: an assessment from the Surgical and Clinical Adhesions Research Study. Br J Obstet Gynaecol 107:855–862

3 Lower AM, Hawthorn RJS, Clark D, Boyd JH, Finlayson AR, Knight AD et al (2004) Adhesion-related readmissions following gynaecological laparoscopy or laparotomy in Scotland: an epidemiological study of 24,046 patients. Hum Reprod 19:1877–1885

4 Diamond MP, Daniell JF, Feste J, Surrey MW, McLaughlin DS, Friedman S et al (1987) Adhesion reformation and de novo adhesion formation after reproductive pelvic surgery. Fertil Steril 47:864–866

5 Pados GA, Devroey P (1992) Adhesions. Curr Opin Obstet Gynecol 4:412–418

6 Monk BJ, Berman ML, Monitz FJ (1994) Adhesions after extensive gynecologic surgery: clinical significance, etiology, and prevention. Am J Obstet Gynecol 170:1396–1403

7 Canis M, Botchorishvili R, Tamburro S, Safi A, Wattiez A, Mage G et al (2001) Adhesion prevention in the surgical treatment of pelvic endometriosis. Gynaecol Endosc 10:99–106

8 Menzies D, Ellis H (1990) Intestinal obstruction from adhesions—how big is the problem? Ann R Coll Surg Engl 72:60–63

9 Diamond MP, Freeman ML (2001) Clinical implications of postsurgical adhesions. Hum Reprod Update 7:567–576

10 Holmdahl L, Eriksson E, Eriksson BI, Risberg B (1998) Depression of peritoneal fibrinolysis during operation is a local response to trauma. Surgery 123:539–544

11 Ivarsson ML, Bergström M, Eriksson E, Risberg B, Holmdahl L (1998) Tissue markers as predictors of postoperative adhesions. Brit J Surg 85:1549–1554

12 Wilson MS, Menzies D, Knight AD, Crowe AM (2002) Demonstrating the clinical and cost effectiveness of adhesion reduction strategies. Colorectal Dis 4:355–360

13 Salum M, Wexner SD, Nogueras JJ, Weiss E, Kouda M, Behrens K et al (2006) Does sodium hyaluronate- and carboxymethylcellulose-based bioresorbable membrane (Seprafilm) decrease operative time for loop ileostomy closure? Tech Coloproctol 10:187–191

14 U.S. Department of Health and Human Services/U.S. Food and Drug Administration (2002) Guidance for resorbable adhesion barrier devices for use in abdominal and/or pelvic surgery. Available online at http://www.fda.gov/cdrh/ode/guidance/1356.pdf

15 diZerega GS (1994) Contemporary adhesion prevention. Fertil Steril 61:219–235

16 Rodgers KE, diZerega GS (2000) Developing pharmacologic agents for adhesion prevention. In: diZerega GS (ed) Peritoneal surgery. Springer-Verlag, New York, pp 441–457

17 Metwally M, Watson A, Lilford R, Vandekerckhove P (2006) Fluid and pharmacological agents for adhesion prevention after gynaecological surgery. Cochrane Database of Systematic Reviews, Issue 2. Art. No.:CD001298. DOI 10.1002/14651858.CD001298.pub3

18 El-Morafi DM, Diamond MP (2003) Are pelvic adhesions preventable? Surg Technol Int 11:222–235

19 Risberg B (1997) Adhesions: preventive strategies. Eur J Surg (Suppl 577):32–39

20 Harris ES, Morgan, RF, Rodeheaver GT (1995) Analysis of the kinetics of peritoneal adhesion formation in the rat and evaluation of potential antiadhesive agents. Surgery 117:663–669

21 Pados G, Camus M, De Munck L, Devroey P (1992) Laparoscopic application of Interceed (TC7). Hum Reprod 7:1141–1143

22 Wallwiener D, Meyer A, Bastert G (1998) Adhesion formation of the parietal and visceral peritoneum: an explanation for the controversy on the use of autologous and alloplastic barriers? Fertil Steril 69:132–137

23 Azziz R, Murphy AA, Rosenberg SM, Patton GW Jr (1991) Use of an oxidized, regenerated cellulose absorbable adhesion barrier at laparoscopy. J Reprod Med 36:479–482

24 Interceed (TC7) Adhesion Barrier Study Group (1989) Prevention of postsurgical adhesions by INTERCEED (TC7), an absorbable adhesion barrier: a prospective randomized multicenter clinical study. Fertil Steril 51:933–938

25 Farquhar C, Vandekerckhove P, Watson A, Vail A, Wiseman D (1999) Barrier agents for preventing adhesions after surgery for subfertility. Cochrane Database of Systematic Reviews, Issue 2. Art. No.:CD000475. DOI 10.1002/14651858.CD000475

26. Larsson B (1996) Efficacy of Interceed in adhesion prevention in gynecologic surgery: a review of 13 clinical studies. J Reprod Med 41:27–34
27. Wiseman DM, Trout JR, Franklin RR, Diamond MP (1999) Metaanalysis of the safety and efficacy of an adhesion barrier (Intercced TC7) in laparotomy. J Reprod Med 44:325–331
28. Nordic Adhesion Prevention Study Group (1995) The efficacy of Interceed(TC7)* for prevention of reformation of postoperative adhesions on ovaries, fallopian tubes, and fimbriae in microsurgical operations for fertility: a multicenter study. Fertil Steril 63:709–714
29. Sawada T, Nishizawa H, Nishio E, Kadowaki M (2000) Postoperative adhesion prevention with an oxidized regenerated cellulose adhesion barrier in infertile women. J Reprod Med 45:387–389
30. Mais V, Ajossa S, Piras B, Guerriero S, Marongiu D, Melis GB (1995) Prevention of de-novo adhesion formation after laparoscopic myomectomy: a randomized trial to evaluate the effectiveness of an oxidized regenerated cellulose absorbable barrier. Hum Reprod 10:3133–3135
31. Keckstein J, Ulrich U, Sasse V, Roth A, Tuttlies F, Karageorgieva E (1996) Reduction of postoperative adhesion formation after laparoscopic ovarian cystectomy. Hum Reprod 11:579–582
32. Diamond MP; The Seprafilm Adhesion Study Group (1996) Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. Fertil Steril 66:904–910
33. Becker JM, Dayton MT, Fazio VW, Beck DE, Stryker SJ Wexner SD et al (1996) Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. J Am Coll Surg 183:297–306
34. Beck DE, Cohen Z, Fleshman JW, Kaufman HS, van Goor H, Wolff BG et al (2003) A prospective, randomized, multicenter, controlled study of the safety of Seprafilm adhesion barrier in abdominopelvic surgery of the intestine. Dis Colon Rectum 46:1310–1319
35. Fazio VW, Cohen Z, Fleshman JW, van Goor H, Bauer JJ, Wolff BG et al (2006) Reduction in adhesive small-bowel obstruction by Seprafilm® adhesion barrier after intestinal resection. Dis Colon Rectum 49:1–11
36. Avital S, Bollinger TJ, Wilkinson JD, Marchetti F, Hellinger MD, Sands LR (2005) Preventing intra-abdominal adhesions with polylactic acid film: an animal study. Dis Colon Rectum 48:153–157
37. Carta G, Cerrone L, Iovenitti P (2004) Postoperative adhesion prevention in gynecologic surgery with hyaluronic acid. Clin Exp Obstet Gynecol 31:39–41
38. Pellicano M, Bramante S, Cirillo D, Palomba S, Bifulco G, Bellato P et al (2003) Effectiveness of autocrosslinked hyaluronic acid gel after laparoscopic myomectomy in infertile patients: a prospective, randomized, controlled study. Fertil Steril 80:441–444
39. Mais V, Bracco GL, Litta P, Gargiulo T, Melis GB (2006) Reduction of postoperative adhesions with an auto-crosslinked hyaluronan gel in gynaecological laparoscopic surgery: a blinded, controlled, randomized, multicentre study. Hum Reprod 21:1248–1254
40. Pellicano M, Guida M, Bramante S, Acunzo G, Di Spiezio Sardo AG, Tommaselli G et al (2005) Reproductive outcome after autocrosslinked hyaluronic acid gel application in infertile patients who underwent laparoscopic myomectomy. Fertil Steril 83:498–500
41. Acunzo G, Guida M, Pellicano M, Tommaselli GA, Di Spiezio Sardo A, Bifulco G et al (2003) Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective, randomized, controlled study. Hum Reprod 18:1918–1921
42. De Iaco PA, Muzzupapa G, Bovicelli A, Marconi S, Bitti SR, M Sansovini et al (2003) Hyaluronan derivative gel (Hyalobarrier® gel) in intrauterine adhesion (IUA) prevention after operative hysteroscopy. Ellipse 19:3–6
43. Guida M, Acunzo G, Di Spiezio Sardo A, Bifulco G, Piccoli R, Pellicano M et al (2004) Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study. Hum Reprod 19:1461–1464
44. Mettler L, Audebert A, Lehmann-Willenbrock E, Schieve K, Jacobs VR (2003) Prospective clinical trial of SprayGel as a barrier to adhesion formation: an interim analysis. J Am Assoc Gynecol Laparosc 10:339–344
45. Johns DA, Ferland R, Dunn R (2003) Initial feasibility study of a sprayable hydrogel adhesion barrier system in patients undergoing laparoscopic ovarian surgery. J Am Assoc Gynecol Laparosc 10:334–338
46. Korrell M (2004) Endometriosis: a common cause of pelvic pain. Adhes News Views 5:18–19
47. Kim KD, Wang JC, Robertson DP, Brodke DS, BenDebba M, Block KM et al (2004) Reduction of leg pain and lower-extremity weakness for 1 year with Oxiplex/SP gel following laminectomy, laminotomy, and discectomy. Neurosurg Focus 17:1–6
48. Lundorff P, Donnez J, Korell M, Audebert AJM, Block K, diZerega GS (2005) Clinical evaluation of a viscoelastic gel for reduction of adhesions following gynaecological surgery by laparoscopy in Europe. Hum Reprod 20:514–520
49. Young P, Johns A, Templeman C, Witz C, Webster B, Ferland R et al (2005) Reduction of postoperative adhesions after laparoscopic gynecological surgery with Oxiplex/AP Gel: a pilot study. Fertil Steril 84:1450–1456
50. Gauwerky JF, Heinrich D, Kubli F (1986) Complications of intraperitoneal dextran application for prevention of adhesions. Biol Res Pregnancy Perinatol 7:93–97
51. Food and Drug Administration MedWatch (2003) Safety Alert—INTERGEL Adhesions Prevention Solution The FDA Safety Information and Adverse Event Reporting Program. Available online at http://www.fda.gov/medwatch/SAFETY/2003/intergel.htm
52. Rosenberg SM, Board JA (1984) High-molecular weight dextran in human infertility surgery. Am J Obstet Gynecol 148:380–385
53. Wiseman DM, Trout JR, Diamond MP (1998) The rates of adhesion development and the effects of crystalloid solutions on adhesion development in pelvic surgery. Fertil Steril 70:702–711
54. Shear L, Swartz C, Shinaberger JA, Barry KG (1965) Kinetics of peritoneal fluid absorption in adult man. N Engl J Med 272:123–127
55. Duffy DM, diZerega GS (1996) Adhesion controversies: pelvic pain as a cause of adhesions, crystalloids in preventing them. J Reprod Med 41:19–26
56. Hart R, Magos A (1996) Laparoscopically instilled fluid: the rate of absorption and the effects on patient discomfort and fluid balance. Gynaecol Endosc 5:287–291
57. Yaacobi Y, Goldberg EP, Habal MB (1991) Effect of Ringer's lactate irrigation on the formation of postoperative abdominal adhesions. J Invest Surg 4:31–36
58. van Westreenen M, van den Tol PM, Pronk A, Marquet RL, Jeekel J, Lequit P (1999) Perioperative lavage promotes intraperitoneal adhesion in the rat. Eur Surg Res 31:196–201
59. Hosie K, Gilbert JA, Kerr D, Brown CB, Peers EM (2001) Fluid dynamics in man of an intraperitoneal drug delivery solution: 4% icodextrin. Drug Delivery 8:9–12
60. Verco SJS, Peers EM, Brown CB, Rodgers KE, Roda N, diZerega G (2000) Development of a novel glucose polymer solution (icodextrin) for adhesion prevention: pre-clinical studies. Hum Reprod 15:1764–1772

61 Rodgers KE, Verco SJS, diZerega GS (2003) Effects of intraperitoneal 4% icodextrin solution on the healing of bowel anastomoses and laparotomy incisions in rabbits. Colorectal Dis 5:324–330
62 diZerega GS, Verco SJS, Young P, Kettel M, Kobak W, Martin D et al (2002) A randomized, controlled pilot study of the safety and efficacy of 4% icodextrin solution in the reduction of adhesions following laparoscopic gynaecological surgery. Hum Reprod 17:1031–1038
63 Brown CB, Luciano AA, Martin D, Peers E, Scrimgeour A, diZerega GS, on behalf of the Adept Adhesion Reduction Study Group (2007) Adept (icodextrin 4% solution) reduces adhesions after laparoscopic surgery for adhesiolysis: a double-blind, randomized, controlled study. Fertil Steril. DOI 10.1016/j.fertnstert.2006.12.084
64 Menzies D, Pascual MH, Walz MK, Duron JJ, Tonelli F, Crowe A et al (2006) Use of icodextrin 4% solution in the prevention of adhesion formation following general surgery: from the multicentre ARIEL Registry. Ann R Coll Surg Engl 88:375–382
65 Sutton C, Minelli L, Garcia E, Korell M, Pouly JL, Pados G et al (2005) Use of icodextrin 4% solution in the reduction of adhesion formation after gynaecological surgery. Gynecol Surg 2:287–296
66 Volz J, Köster S, Weiss M, Schmidt R, Urbaschek R, Melchert F et al (1996) Pathophysiologic features of a pneumoperitoneum at laparoscopy: a swine model. Am J Obstet Gynecol 174:132–140
67 Volz J, Köster S, Leweling H (1997) Surgical trauma and metabolic changes induced by surgical laparoscopy versus laparotomy. Gynecol Endosc 6:1–6
68 West MA, Hackam DJ, Baker J, Rodriguez JL, Bellingham J, Rotstein OD (1997) Mechanism of decreased in vitro murine macrophage cytokine release after exposure to carbon dioxide: relevance to laparoscopic surgery. Ann Surg 226:179–190
69 Ryan GB, Grobéty J, Majno G (1973) Mesothelial injury and recovery. Am J Pathol 71:93–112
70 Taskin O, Buhur A, Birincioglu M, Burak F, Atmaca R, Yilmaz I et al (1998) The effects of duration of CO_2 insufflation and irrigation on peritoneal microcirculation assessed by free radical scavengers and total glutathion levels during operative laparoscopy. J Am Assoc Gynecol Laparosc 5:129–133
71 Taskin O, Sadik S, Onoglu A, Gokdeniz R, Yilmaz I, Burak F et al (1999) Adhesion formation after microlaparoscopic and laparoscopic ovarian coagulation for polycystic ovary disease. J Am Assoc Gynecol Laparosc 6:159–163
72 Molinas CR, Koninckx PR (2000) Hypoxaemia induced by CO_2 or helium pneumoperitoneum is a co-factor in adhesion formation in rabbits. Hum Reprod 15:1758–1763
73 Binda MM, Molinas CR, Mailova K, Koninckx PR (2004) Effect of temperature upon adhesion formation in a laparoscopic mouse model. Hum Reprod 19:2626–2632
74 Binda MM, Molinas CR, Hansen P, Koninckx PR (2006) Effect of desiccation and temperature during laparoscopy on adhesion formation in mice. Fertil Steril 86:166–175
75 Parker MC, Ellis H, Moran BJ, Thompson JN, Wilson MS, Menzies D et al (2001) Postoperative adhesions: ten-year follow-up of 12,584 patients undergoing lower abdominal surgery. Dis Colon Rectum 44:822–830
76 Ellis H (2004) Medicolegal consequences of adhesions. Hosp Med 65:348–350
77 Ellis H (2001) Medicolegal consequences of postoperative intra-abdominal adhesions. J R Soc Med 94:331–332
78 Trew G (2006) Postoperative adhesions and their prevention. Rev Gynaecol Perinat Pract 6:47–56
79. Wiseman D (2003) Adhesions and informed consent: patients awareness of adhesions prior to surgery. In: Proceedings of the 6th International Symposium on Peritoneum (PAX), Amsterdam, The Netherlands, April 2003. PAX Abstracts pp 21:VII(4)
80 Wiseman D (2003) Obtaining informed consent: patient awareness of adhesions. Adhes News Views 4:10–12
81 Pownall M (1999) Tissue damage is commonest cause of surgical negligence suits. BMJ 318:692
82. Swank DJ, Swank-Bordewijk SC, Hop WC, van Erp WF, Janssen IM, Bonjer HJ et al (2003) Laparoscopic adhesiolysis in patients with chronic abdominal pain: a blinded randomised controlled multi-centre trial. Lancet 361:1247–1251
83 van der Krabben AA, Dijkstra FR, Nieuwenhuijzen M, Reijnen MMPJ, Schaapveld M, van Goor H (2000) Morbidity and mortality of inadvertent enterotomy during adhesiotomy. Br J Surg 87:467–471
84. Ferriman A (2000) Laparoscopic surgery: two thirds of injuries initially missed. BMJ 321:788
85 Skene L, Smallwood R (2002) Informed consent: lessons from Australia. BMJ 324:39–41
86. DeWilde RL, Trew G, on behalf of the Expert Adhesions Working Party of the European Society of Gynaecological Endoscopy (ESGE) (2007) Postoperative abdominal adhesions and their prevention in gynaecological surgery. Expert consensus position. Gynecol Surg. DOI 10.1007/s10397-007-0338-x

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 8

FDA approves ADEPT® Adhesion Reduction Solution (4% Icodextrin Solution)

01 Aug 2006

ADEPT offers Novel Fluid-Based Approach for Reducing Post-Surgical Adhesions

NOTTINGHAM, UK, and DEERFIELD, ILLINOIS, August 1, 2006 – Innovata plc and Baxter Healthcare Corporation announced today that the U.S. Food and Drug Administration (FDA) has approved ADEPT® Adhesion Reduction Solution for use in gynaecological laparoscopic procedures in the United States.

ADEPT is indicated for intraperitoneal use as an adjunct to good surgical technique for the reduction of post-surgical adhesions in patients undergoing gynaecological laparoscopic adhesiolysis. ADEPT is a 4% icodextrin solution that has been used for adhesion reduction in Europe since 2000.

ADEPT has been studied in three randomised, controlled U.S. clinical trials involving a total of 548 patients undergoing gynaecological laparoscopic surgery with a follow-up (second look) laparoscopic procedure after the initial procedure. In the pivotal study, for the patients in the ADEPT group, 45.4% were defined as a "clinical success" compared to 35.6% in the control group. Clinical success was defined as a decrease in the number of adhesions between the first (baseline) and second laparoscopies. Patients in the ADEPT group had significantly (p=0 016) fewer sites with adhesions at second-look compared to first-look adhesiolysis laparoscopy.

Adhesions are abnormal attachments between tissues or organs. Gynaecological adhesions may cause pain, secondary infertility or other complications in women.

"This is a significant development for patients with adhesion-related disorders and the surgeons who are managing those patients," said Thomas Lyons, MD, of Atlanta, GA, who served as one of the clinical investigators for the U.S. trials. "This is currently the only product which has approval for laparoscopic use, making it doubly helpful since laparoscopic surgery is a better solution for adhesions than traditional open surgery. As a gynaecologic surgeon who works in this area I am excited for our patients and look forward to improved outcomes for our patients."

ADEPT is the first and only approved fluid-based approach for adhesion reduction in gynaecological laparoscopic adhesiolysis in the United States. ADEPT is a liquid, which means it can be delivered directly and rapidly to the site through a laparoscopic port during surgery.

Developed by Innovata, ADEPT is licensed to Baxter on a global basis. Baxter's BioSurgery business will launch ADEPT in the United States in the fourth quarter. Baxter's BioSurgery business develops and commercialises biosurgery products used in the areas of haemostasis, tissue sealing and tissue repair.

"ADEPT is one of the most important gynaecological surgical device developments in the last decade, filling a niche where there are limited options," said Kieran Murphy, chief executive officer of Innovata. "The U.S. FDA approval will allow the product to be used by surgeons in the world's largest market, significantly expanding its presence beyond Europe. We look forward to working with our partners at Baxter to prepare for the commercial launch."

"Through its use on more than 150,000 patients in Europe and in U.S. clinical trials, ADEPT has demonstrated its convenience, and safety and efficacy in reducing the number of adhesions following surgery," said Gordon Sutherland, general manager of BioSurgery for Baxter. "We believe the anti-adhesion market has been underserved, and are looking forward to providing physicians with an easy-to-use solution."

Contacts:

Innovata plc **Tel: 0115 974 7474**
Kieran Murphy, Chief Executive Officer
Peter Shennan, Finance Director

Baxter
Media: Deborah Spak **Tel: (847) 948-2349**
Investors: Mary Kay Ladone **Tel: (847) 948-3371**

Financial Dynamics **Tel. 020 7831 3113**
Sarah MacLeod/Anna Keeble

Notes to Editors

Adept
ADEPT contains icodextrin derived from cornstarch and is contraindicated in patients with known or suspected allergy to icodextrin and similar polymers. ADEPT is contraindicated in laparotomy, in cases involving bowel resection or repair, or appendectomy and in surgical cases with frank abdomino-pelvic infection. There have been rare reports of sterile peritonitis following the use of icodextrin. Leakage of ADEPT from port sites may lead to wound healing complications; meticulous fascial closure is advised. There have been rare reports of hypersensitivity reactions, pulmonary oedema, pulmonary effusion and arrhythmia. In such cases, the risk/benefit profile should be assessed before use of ADEPT.

Innovata Plc
Innovata plc specialises in the development of pulmonary products for the treatment of respiratory disorders and other serious diseases. Using its proprietary dry powder inhaler and drug formulation technologies, the company has developed a pipeline of revenue-generating/marketed and clinical-stage products. In addition, the company has a portfolio of non-pulmonary products with growing revenues. Innovata has established development and marketing partnerships with a number of pharmaceutical companies including Baxter, Merck KGaA, UCB and Otsuka. For further information, please see www.innovataplc.com.

Baxter Healthcare Corporation
Baxter Healthcare Corporation is the principal U.S. operating subsidiary of Baxter International Inc. (NYSE: BAX). Baxter assists healthcare professionals and their patients with treatment of complex medical conditions, including cancer, haemophilia, immune disorders, kidney disease and trauma. The company applies its expertise in medical devices, pharmaceuticals, and biotechnology to make a meaningful difference in patients' lives. For more information about Baxter, please visit www.baxter.com.

This release includes forward-looking statements concerning the availability and use of ADEPT. The statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those in the forward-looking statements: completion of final steps in product development, including scaling up production, including satisfactory quality and regulatory work, commercial acceptance of the product; and other risks identified in the company's most recent filing on Form 10-Q and other SEC filings, all of which are

available on the company's web site The company does not undertake to update its forward-looking statements

ADEPT® is a registered trademark of Innovata plc.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 9

Baxter

adept®

Adhesion Reduction Solution (4% Icodextrin)

INFORMATION FOR PRESCRIBERS

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN.

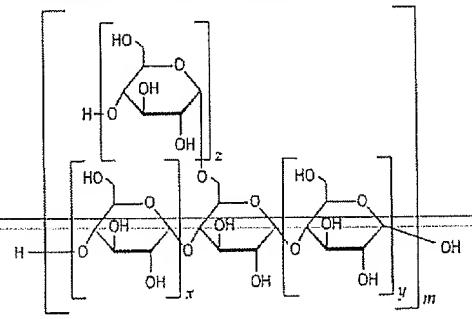
CAUTION: DO NOT USE UNLESS SOLUTION IS CLEAR AND CONTAINER IS UNDAMAGED.

CAUTION: ADEPT® is for direct intraperitoneal administration only. **NOT** FOR INTRAVENOUS (IV) ADMINISTRATION.

I. DEVICE DESCRIPTION AND MECHANISM OF ACTION

ADEPT® (4% Icodextrin) Adhesion Reduction Solution is a single use, sterile, clear, colorless-to-pale yellow fluid for intraperitoneal administration containing icodextrin at a concentration of 4% w/v in an electrolyte solution. Icodextrin is a cornstarch-derived, water-soluble branched glucose polymer linked by alpha (1-4) and less than 10% alpha (1-6) glucosidic bonds with a weight-average molecular weight between 13,000 and 19,000 Daltons and a number-average molecular weight between 5,000 and 6,500 Daltons. The representative structural formula of Icodextrin is:

Figure 1: Structural Formula of Icodextrin



Each 1 liter of ADEPT® contains:

Icodextrin	40 g
Sodium Chloride	5.4 g
Sodium Lactate	4.5 g
Calcium Chloride	257 mg
Magnesium Chloride	51 mg

Theoretical osmolarity 278 milliosmoles per liter

Ionic composition (approximately) per liter:

Sodium	133 mmol
Calcium	1.75 mmol
Magnesium	0.25 mmol
Chloride	96 mmol
Lactate	40 mmol

ADEPT® is packaged in flexible polyvinylchloride bags containing 1 L or 1.5 L of solution. When stored at temperatures below 30°C ADEPT® has a shelf life of 24 months. ADEPT® should not be refrigerated or frozen.

MECHANISM OF ACTION AND CLEARANCE

Icodextrin, as an alpha (1-4)-linked glucose polymer, is similar in structure to carbohydrates which occur physiologically, e.g. glycogen. When administered intraperitoneally as a 4% solution, icodextrin functions as a colloid osmotic agent. This colloidal osmotic action of icodextrin allows the retention of a reservoir of fluid within the peritoneal cavity for 3-4 days.[1]

ADEPT® is believed to perform its function through a physical effect by providing a temporary separation of peritoneal surfaces by hydroflotation as a result of maintaining a fluid reservoir. This minimizes tissue apposition during the critical period of fibrin formation and mesothelial regeneration following surgery, thereby providing a barrier to adhesion formation.

Pharmacokinetics of Icodextrin

Absorption

Absorption of icodextrin from the peritoneal cavity follows zero-order kinetics, consistent with convective transport via the lymphatic pathways. Studies in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) indicate that a median of 40% of the instilled icodextrin was absorbed from the peritoneal solution during a 12 hour dwell [2]

Metabolism and Elimination

When given intraperitoneally, the icodextrin polymer is not metabolized significantly in the peritoneal cavity but is slowly transferred into the systemic circulation by peritoneal lymphatic drainage In the systemic circulation icodextrin is rapidly metabolized by alpha-amylase to lower molecular weight oligosaccharides, which along with icodextrin, are eliminated by renal excretion The rate of clearance of icodextrin from the systemic circulation has been estimated to be equal to glomerular filtration rate

II. INDICATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

INDICATION FOR USE

ADEPT® Adhesion Reduction Solution is indicated for use intraperitoneally as an adjunct to good surgical technique for the reduction of post-surgical adhesions in patients undergoing gynecological laparoscopic adhesiolysis.

CONTRAINDICATIONS

ADEPT® is contraindicated:

- In patients with known or suspected allergy to cornstarch based polymers e g Icodextrin, or with maltose or isomaltose intolerance. or with glycogen storage disease
- In the presence of frank infection (e g. peritonitis) in the abdomino-pelvic cavity.
- In procedures with laparotomy incision. Serious post-operative wound complications including dehiscence and cutaneous fistula formation have been reported from clinical experience outside the US when ADEPT® was used in surgical cases with laparotomy incision
- In procedures involving bowel resection or repair, or appendectomy Anastomotic failure, ileus and peritonitis following procedures involving bowel resection and instillation of ADEPT® have been reported from clinical experience outside of the US

WARNINGS

- There have been rare reports of sterile peritonitis following the use of icodextrin. The differential diagnosis of abdomino-pelvic pain following instillation of ADEPT® should include peritoneal cavity infection, perforated bowel or other viscous, intraperitoneal bleeding, and other life threatening post-operative complications in addition to sterile peritonitis
- Leaking ADEPT® fluid through laparoscopic port sites post-operatively is associated with wound complications such as subcutaneous fluid collection, skin separation and infection Meticulous closure of fascia may help reduce wound complications related to fluid extravasation following gynecologic laparoscopy surgery.
- There have been rare reports of hypersensitivity reactions in patients treated with ADEPT®. Anaphylaxis has been reported in a few patients.
- There are rare reports of pulmonary edema, pulmonary effusion and arrhythmia from clinical experience with ADEPT® outside of the US These cases tended to occur in elderly or otherwise debilitated patients (e g cancer patients) The potential benefit of ADEPT® for adhesion prevention should be carefully weighed against the risk of serious complications in patients with serious co-morbidities.
- Foreign body reactions may occur with ADEPT®, as with any implanted material

PRECAUTIONS

- ADEPT® is for direct intraperitoneal administration only. **NOT** for intravenous (IV) administration
- ADEPT® is not indicated as a delivery system for intraperitoneal drugs such as antibiotics and chemotherapeutic agents
- The effectiveness of ADEPT® has not been established for longer term clinical outcomes following gynecological surgery, e g. pregnancy and pain
- Self-limited vulvar swelling is a known side-effect of instilling large volumes of fluid into the abdomino-pelvic cavity Most cases resolve within one week of surgery When swelling is associated with urinary retention, catheterization may be necessary.
- Maltose metabolites of icodextrin may interfere with blood glucose measurement in diabetic patients who use rapid blood glucose systems that are not glucose specific

- The safety and effectiveness of ADEPT® have not been evaluated:
  - in patients less than 18 years of age;
  - in pregnancy;
  - when volume left in peritoneal cavity exceeds 1 L;
  - in patients with abnormal liver and/or renal function; or
  - in cases where there is a breach in the vaginal epithelium;

III. ADVERSE EVENTS

Postmarketing Passive Surveillance Outside of US

ADEPT® Adhesion Reduction Solution was approved for use in Europe in October 1999. A Europe-wide multicenter registry for evaluating clinical experience using ADEPT® was launched in 2000. The ARIEL registry was intended to capture the experience of surgeons using ADEPT® in both general and gynecological surgery. Data were collected between September 2000 and December 2003.

A total of 4620 patients were enrolled in the ARIEL registry. Of these, 2882 were gynecology patients (72% laparoscopy) and 1738 were general surgery patients (85% laparotomy). Adverse events were reported in 7.5% gynecological laparoscopy and 13.9% gynecological laparotomy patients compared with 16.7% general surgery laparoscopy and 30.6% general surgery laparotomy patients.[3,4] Table 1 summarizes key events. These events are presented regardless of the reporting surgeon's causality assessment.

Table 1. Selected Key Adverse Events from ARIEL Registry[a]

	Gynecology N=2882			General Surgery N=1738		
Adverse Event	Laparoscopy	Laparotomy	Not known	Laparoscopy	Laparotomy	Not known
Wound Complication[b]	13	15	1	2	68	4
Vulvar Swelling	7	1	3	0	1	0
Failed anastamosis	0	0	0	4	33	0
Ileus	3	2	1	4	46	1
Pain	15	10	2	4	9	0
Pulmonary Complication	0	3	0	1	7	0
Allergic Reaction[c]	0	2	0	0	2	0

a Adverse events in this table were tabulated using a different methodology from that of Sutton[3] et al., and Mendes[4] et al. Therefore, numbers of events in different categories may not correspond exactly with the numbers in the published literature.

b "Wound complication" includes subcutaneous fluid collection near the incision/port site.

c Icodextrin has been associated with skin reactions such as rash. Three of the cases in the above table were more serious events and had systemic involvement.

US Clinical Trial Experience

ADEPT® has been studied in three randomized, controlled US clinical trials involving a total of 548 patients undergoing gynecological laparoscopic surgery with second-look laparoscopy 4-12 weeks after the initial procedure. In all three studies, the control device was Lactated Ringer's Solution (LRS). Two pilot studies to obtain preliminary safety data enrolled a total of 99 (59 ADEPT® treated, 40 LRS) patients. The third US clinical trial of ADEPT® was a double-blind pivotal study in which 449 subjects (227 ADEPT® treated, 222 LRS) were treated.

Pilot Studies:

In the first pilot study (CLASSIC), 62 subjects (34 ADEPT® and 28 LRS) were evaluated. Approximately two liters of solution were used for irrigation intraoperatively, and one liter was instilled at the end of the procedure. Two cases of moderate labial or vulvar swelling were reported in the ADEPT® subjects. There were no LRS-related adverse events.

In the second pilot study (RAPIDS), 37 subjects (25 ADEPT® and 12 LRS) were evaluated. Approximately 1500-1900 mL of solution were used for irrigation intraoperatively. An average 2L of ADEPT® vs. 1300mL LRS was instilled at the end of the procedure. The objective of this study was to evaluate the safety of larger volumes of ADEPT® as a post-operative instillate. One case of labial swelling was reported in an ADEPT® subject.

Pivotal Clinical Trial:

In the double-blind, pivotal study, ADEPT® or LRS was used as an intra-operative irrigant (100mL every 30 minutes) and 1L was instilled into the peritoneal cavity at the end of the procedure. 221 (97.4%) ADEPT® patients reported a total of 1065 events compared to 218 (98.2%) LRS patients who reported 1047 events.

Table 2 presents adverse events reported in $\geq$ 5% of patients (regardless of causality) in the pivotal trial.

Table 2: Pivotal Study Most Frequent Adverse Events (i.e. those reported by at least 5% of patients in either group, regardless of causality) – Intention-to-Treat (ITT) Population

	ADEPT®		LRS	
	Number of patients reporting	Number of reports	Number of patients reporting	Number of reports
Total number of patients at risk	227		222	
Post procedural pain	192 (84.6%)	223	194 (87.4%)	233
Headache	81 (35.7%)	131	72 (32.4%)	127
Nausea	39 (17.2%)	41	37 (16.7%)	41
Leaking from Port Sites Post-procedure	31 (13.7%)	31	30 (13.5%)	30
Dysmenorrhea	30 (13.2%)	32	26 (11.7%)	34
Constipation	24 (10.6%)	26	23 (10.4%)	24
Pelvic pain	23 (10.1%)	32	21 (9.5%)	21
Arthralgia	20 (8.8%)	22	19 (8.6%)	19
Flatulence	19 (8.4%)	19	17 (7.7%)	19
Urinary tract infection	16 (7.0%)	17	12 (5.4%)	13
Abdominal pain	15 (6.6%)	26	19 (8.6%)	23
Dysuria	15 (6.6%)	16	8 (3.6%)	9
Nasopharyngitis	15 (6.6%)	15	18 (8.1%)	18
Vaginal bleeding	14 (6.2%)	15	5 (2.3%)	5
Abdominal distension	13 (5.7%)	13	10 (4.5%)	10
Post procedural nausea	13 (5.7%)	13	20 (9.0%)	20
Pyrexia	13 (5.7%)	13	7 (3.2%)	7
Vomiting	13 (5.7%)	13	22 (9.9%)	22
Labial, Vulvar or Vaginal swelling	13 (5.7%)	13	1 (0.45%)	1
Back pain	12 (5.3%)	15	12 (5.4%)	13
Insomnia	12 (5.3%)	14	8 (3.6%)	8
Cough	10 (4.4%)	10	12 (5.4%)	13
Diarrhea	3 (1.3%)	3	13 (5.9%)	15

In the pivotal study, the most frequently occurring (report incidence as % of number of patients) treatment-related adverse events between surgeries were post procedural leaking from port sites, labial, vulvar or vaginal swelling and abdominal distension

IV. CLINICAL STUDIES

ADEPT® has been studied in the USA in two pilot studies and one double-blind, pivotal study in female patients undergoing gynecological laparoscopic surgery with a planned second look laparoscopy. The studies were conducted to evaluate the safety and effectiveness of the device as an adjunct to good surgical technique in the reduction of post-surgical adhesions in comparison to (LRS). ADEPT® or LRS was used as an intra-operative irrigant (100 mL every 30 minutes) in all studies; in the pivotal study, 1L of ADEPT® or LRS was instilled into the peritoneal cavity at the end of the surgical procedure. In the pilot studies, 1L in the first study and up to 2L in the second study were instilled at the end of surgery. In all three studies, the incidence, extent and severity of adhesions were assessed at 23 prospectively determined anatomical sites, using established adhesion scoring methods at baseline surgery (prior to adhesiolysis) and at second look laparoscopy. Safety was evaluated based on adverse events and clinical laboratory tests.

For both pilot studies, second look laparoscopy took place 6-12 weeks after the initial surgery. In both of these studies, there was a greater reduction in the number of sites with adhesions, and the extent and severity of adhesions in the ADEPT® subjects compared to the LRS subjects. However, these differences were not statistically significant, which may be due in part to the relatively small numbers of subjects in these studies.

PIVOTAL STUDY

The pivotal study was a comparative, double-blind, randomized, multicenter study in the USA. A total of 449 female patients aged eighteen or over were enrolled for whom laparoscopic peritoneal cavity surgery was planned for a gynecological procedure which included adhesiolysis and who agreed to undergo second look laparoscopy as part of their treatment plan at 4-8 weeks after the initial surgery. The patients had to have adhesions at three or more of the 23 pre-specified anatomical sites and adhesions at three or more of the anatomical sites had to be lysed during the surgery.

Objectives

The study objectives were to determine the effectiveness and safety of ADEPT® when used as an intraoperative washing solution with a postoperative instillate in the reduction of post-surgical adhesions after laparoscopic surgery for adhesiolysis, compared with LRS.

Inclusion Criteria:

- willing, able to and having freely given written consent to participate in the study and abide by its requirements;
- female patients aged eighteen and over, in good general health including ASA (American Society of Anesthesiologists) score of 2 or less;

- laparoscopic peritoneal cavity surgery is planned for a gynecologic procedure which includes adhesiolysis; and
- patient agrees to planned second look laparoscopy for this study 4-8 weeks after the initial surgical procedure

Exclusion Criteria (pre-operative):

- current pregnancy including ectopic pregnancy;
- SGOT, SGPT and/or bilirubin > 20% above the upper range of normal and considered clinically significant;
- BUN and creatinine > 30% above the upper range of normal and considerad clinically significant;
- concurrent use of systemic corticosteroids, antineoplastic agents and/or radiation;
- active pelvic or abdominal infection;
- known allergy to starch-based polymers; and
- additional surgical procedure (non-OB/GYN) planned to be performed during the laparoscopic procedure

Exclusion Criteria (intra-operative):

- clinical evidence of cancer;
- clinical evidence of pregnancy including ectopic pregnancy;
- use during this procedure of any approved or unapproved product for the purpose of preventing adhesion formation;
- fewer than 3 of the available anatomical study sites contain adhesions;
- less than three of the anatomical sites are lysed;
- if the procedure needs to be performed by a laparotomy (decision made after laparoscopy has commenced);
- if any of the anatomical sites being scored for the purposes of this study are being removed during surgery;
- if all of the available anatomical sites cannot be visualized and recorded on the video tape during the surgery; and
- any unplanned surgery which involves opening of the bowel (excluding appendectomy).

Study Hypotheses

There were three co-primary outcome measures, each with a respective hypothesis:

(1) The first co-primary endpoint for the pivotal study was the difference (for an individual study subject) in the number of adhesion sites between baseline and second look laparoscopy. For subjects with ten or fewer adhesions lysed at surgery, an individual patient success was defined as a decrease of at least 3 sites with adhesions between baseline and second look laparoscopy. For subjects with more than ten adhesions lysed at baseline, individual patient success was defined as a decrease in adhesion sites of at least 30% between baseline and second look laparoscopy. The study hypothesis for the first co-primary endpoint was that the lower bound of the 95.2% CI around the difference in success rates will be above 5%.

(2) The second co-primary endpoint was the difference (for an individual study subject) in the number of adhesion sites between baseline and second look laparoscopy. In the hypothesis for this endpoint, patients served as their own control. The study hypothesis for the 2nd co-primary endpoint was that ADEPT® treated subjects would have fewer sites with adhesions at second look laparoscopy than they had at baseline.

(3) The third co-primary endpoint was the difference (for an individual subject) in the number of dense adhesion sites between baseline and second look laparoscopy. For the 3rd co-primary endpoint, success for a subject was defined as any reduction in dense adhesion sites between baseline and second look laparoscopy. The study hypothesis for the 3rd co-primary endpoint was that the success rate for ADEPT®-treated subjects would be greater than that for LRS treated subjects.

Secondary Endpoints

The study had the following pre-specified secondary endpoints. No hypothesis tests were specified for these endpoints.

Incidence of sites with adhesions
Severity of sites with adhesions
Extent of sites with adhesions
American Fertility Society (AFS) score
Modified AFS score
Reformed adhesions
De novo adhesions
Abdominal wall adhesions
Visceral adhesions
Visual Analog Scale (VAS) score for pelvic pain

Figure 2 is a patient accounting of all subjects in the pivotal study, including the initial screen

Figure 2: Patient Accounting

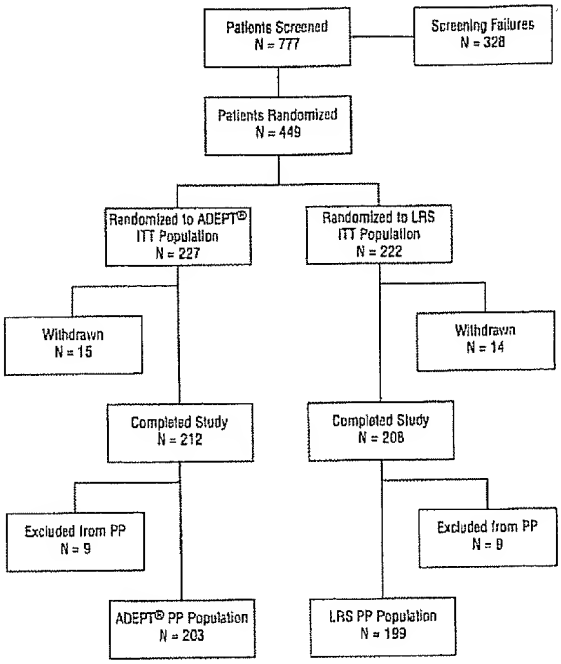


Table 3: Pivotal Study Demographics and Baseline Data, ITT

		ADEPT®	LRS
No of patients randomized (ITT)		227	222
Demographics ± s d			
Age, yr		32.6 ± 5.9	32.3 ± 5.7
Height, in (n)		64.7 ± 2.7 (225)	64.2 ± 2.8 (221)
Weight, lb (n)		153.2 ± 36.9 (225)	152.0 ± 35.0 (220)
Race	Caucasian	160 (70.5%)	144 (64.9%)
n (%):	East Asian	3 (1.3%)	7 (3.2%)
	African American	32 (14.1%)	32 (14.4%)
	Hispanic	24 (10.6%)	35 (15.8%)
	Oriental	3 (1.3%)	1 (0.5%)
	Other	5 (2.2%)	3 (1.4%)
Base vital signs			
Systolic blood pressure, mmHg (n)		114.9 ± 12.1 (224)	114.5 ± 11.8 (221)
Diastolic blood pressure, mmHg (n)		71.5 ± 8.8 (224)	71.4 ± 8.8 (221)
Heart rate, bpm (n)		73.1 ± 8.8 (224)	73.2 ± 8.3 (218)
Primary diagnosis n (%)			
Pelvic pain		152 (67.0%)	134 (60.4%)
Endometriosis		94 (41.4%)	93 (41.9%)
Infertility		115 (50.7%)	127 (57.2%)
Adhesions		126 (55.5%)	127 (57.2%)
Others		36 (15.9%)	43 (19.4%)
Medical history n (%)			
No of patients with resolved medical conditions		192 (84.6%)	191 (86.0%)
No of patients with ongoing medical conditions		224 (98.7%)	219 (98.6%)
No of patients with surgical history		205 (90.3%)	196 (88.3%)
Baseline assessment of adhesions			
Number of Sites with Adhesions		10.27 ± 4.26	10.34 ± 4.39
Number of Sites with lysed Adhesions		8.69 ± 4.15	8.46 ± 4.02
Number of Sites with dense Adhesions		6.17 ± 4.74	6.23 ± 5.26
Number of Sites with lysed dense Adhesions		5.35 ± 4.56	5.15 ± 4.46
Baseline AFS score for infertility subgroup (PP)		9.52 ± 10.39	8.60 ± 9.99
Baseline mAFS score (PP)		2.71 ± 2.47	2.81 ± 2.93
Endometriosis n (%)			
Present at baseline		140 (61.7%)	135 (60.8%)
Treated		138 (60.8%)	135 (60.8%)
Others			
Operative Time (mins) (median) (ITT)		85.0	88.0
Days between first and second look surgery (ITT)		39.9 ± 10.3	39.9 ± 10.7
Average volume of solution lavaged and instilled, ml (min-max)		3,502 (1,300-12,000)	3,570 (1,300-12,000)

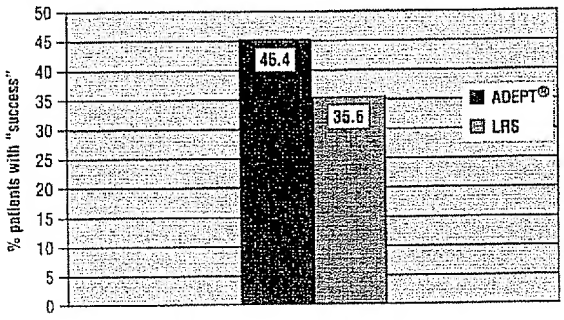
Table 3 shows that the study arms were well balanced Almost all sites with adhesions were lysed (on average 10 at baseline with 9 lysed for both groups). Similarly, almost all sites with dense adhesions were lysed (on average 6 at baseline and 5 lysed). The study population had a fairly substantial adhesion burden with an average of 10 sites per subject and 6 sites with dense adhesions per subject.

Pivotal Study Results

Primary Effectiveness Endpoints

First Co-Primary Endpoint: 45 4% of the patients in the ADEPT® group were defined as a "clinical success" compared to 35 6% in the LRS group (p=0.016, two-tailed test) (Table 4). However, the lower bound of the 95 2% CI around the difference in success rates (0 7%) is below the pre-specified 5% target. Data is presented as intent-to-treat (ITT). (see Figure 3)

Figure 3: Pivotal Study First primary effectiveness endpoint (percentage of patients achieving "success") – Intention to Treat population



Second Co-Primary Endpoint: Patients in the ADEPT® group had significantly fewer sites with adhesions at second look compared to first look laparoscopy (p<0.001). The 95 2% confidence intervals were less than zero for both the ADEPT® treated patients (-2 83 to -1.62) and the LRS-treated patients (-2.24 to -0 96). There was a significantly greater reduction in the number of sites with adhesions in the ADEPT® treated patients compared with the LRS group (p=0 047, two-tailed test)

Third Co-Primary Endpoint: In the ADEPT® group, 50% of patients had fewer sites with dense adhesions at second look (mean reduction 1.19 ± 3.43, p<0 001); in the LRS group, the figure was similar (49%) (see Table 4). There was no statistically significant difference between treatments (p=0.73)

Table 4: Pivotal Study Primary Effectiveness Endpoints – Intention-to-Treat population

First primary effectiveness endpoint

	ADEPT®	LRS
Total number of patients	227	222
Success[a]		
Number reporting	103 (45.4%)	79 (35.6%)
Difference in % of patients with success	9.8	
Se	4.6	
95.2 CI for % of patients with success	(0.7, 18.9)	
Odds ratio[b]	1.64	
95.2% CI for odds ratio	(1.09, 2.46)	
p-value for treatment	0.016*	

a Success was achieved if the number of sites with adhesions decreased by at least the larger of three sites or 30% of the number of sites lysed

b Estimated from a logistic regression model with factors for treatment group and center A value >1 favors ADEPT® The odds ratio (95.2% CI) using exact methods was 1.61 (1.06, 2.46)

* Statistically significant at the 4.8% level, two-tailed

Second primary effectiveness endpoint

	ADEPT®	LRS
Total number of patients	227	222
Number of sites with adhesions		
First look (mean±sd)	10.27±4.26	10.34±4.39
Second look (mean±sd)	7.88±4.64	8.49±4.98
Change from first to second look (mean±sd)	-2.40±3.66	-1.86±3.35
LS mean for change[a] (95.2% CI)	-2.22 (-2.83, -1.62)	-1.60 (-2.24, -0.95)
p-value for change	<0.001***	<0.001***
Difference between LS means[b]	-0.62	
Se	0.31	
95.2% CI	(-1.24, -0.004)	
p-value for treatment	0.047	

a Estimated from an ANCOVA model with factors for treatment group and center and a covariate for first look score

b A negative difference favors ADEPT®

*** Statistically significant at the 0.1% level

Third primary effectiveness endpoint

	ADEPT®	LRS
Total number of patients	227	222
Number of sites with dense adhesions		
First look (mean±sd)	6.17±4.74	6.23±5.26
Second look (mean±sd) (n)	5.02±4.60 (212)	5.25±5.26 (206)
Change from first to second look (mean±sd) (n)	-1.19±3.43 (212)	-1.01±3.24 (206)
p-value for change	<0.001	<0.001
Number of patients with fewer dense adhesions at second look	114 (50.2%)	109 (49.1%)
Odds ratio[a]	1.07	
95.2% CI for odds ratio	(0.72, 1.59)	
p-value for treatment	0.73	

a Estimated from a logistic regression model with factors for treatment group and center A value >1 favors ADEPT® The odds ratio (95.2% CI) using exact methods was 1.07 (0.71, 1.61).

Secondary effectiveness (*per protocol* population)

In all (10) secondary effectiveness variables, use of ADEPT® appeared to provide benefits beyond those provided by control, although not all to a statistically significant level Both groups showed a reduction in adhesion burden, but this was consistently greater in the ADEPT® group

These secondary endpoints provide supportive evidence for the primary endpoints and have not been adjusted for multiplicity (see Tables 5 to 8). When a multiplicity adjustment is applied to the data, one secondary endpoint remains statistically significant in favor of ADEPT®: the subgroup of patients presenting with a primary diagnosis of infertility showed a statistically significant reduction in AFS score compared to control (p<0.05)

Table 5 : Pivotal Study Secondary Effectiveness Endpoints (PP) for Adhesions at Anatomical Sites

Endpoint / Variable	ADEPT® (n=203)	LRS (n=199)	p-value*
Incidence of sites with adhesions			
Change from 1st to 2nd look (mean ± s.d.)	-2.64 ± 3.66	-2.02 ± 3.19	0.039
% patients with reduction	76.4%	69.3%	0.121
Change from 1st to 2nd look excluding non-lysed sites (mean ± s.d.)	-2.64 ± 3.66	-2.02 ± 3.19	0.068
% patients with four or fewer sites with adhesions at 2nd look	32.0	26.1	0.510
Shift analysis - % patients with 2nd look incidence grouped into 4 categories	0: 4.9 1-4 27.1 5-9 36.0 ≥10 32.0	0: 4.5 1-4 23.6 5-9 31.7 ≥10 40.2	0.173
Severity of sites with adhesions			
% change from 1st to 2nd look per patient (mean ± s.d.)	-24.2 ± 45.2	-21.5 ± 41.0	0.415
% patients with reduction	72.9%	69.8%	0.446
Extent of sites with adhesions			
% change from 1st to 2nd look per patient (mean ± s.d.)	-26.9 ± 51.4	-21.8 ± 48.5	0.240
% patients with reduction	77.3%	69.8%	0.084
Modified AFS score			
Change from 1st to 2nd look (mean ± s.d.)	-0.67 ± 1.54	-0.48 ± 1.61	0.094
% patients with reduction	70.4%	69.8%	0.722

* not adjusted for multiplicity.

Table 6: Pivotal Study Secondary Effectiveness Endpoints (PP) for Subgroup of Patients with a Primary Diagnosis of Infertility

Endpoint / Variable	ADEPT® (n=102)	LRS (n=112)	p-value*
AFS score			
Change from 1st to 2nd look for patients with a primary diagnosis of infertility (mean ± s.d.)	-3.46 ± 6.77	-1.10 ± 6.36	0.011
% patients with reduction for patients with a primary diagnosis of infertility	52.9%	30.4%	0.001
Shift analysis - % patients with 2nd look scores grouped into 4 categories for patients with a primary diagnosis of infertility	minimal: 68.6 mild: 10.8 moderate: 11.8 severe: 8.8	minimal: 59.8 mild: 13.4 moderate: 15.2 severe: 11.6	0.041

* not adjusted for multiplicity.

Table 7: Pivotal Study Secondary Effectiveness Endpoints (PP) for Types of and Location of Adhesions

Endpoint / Variable	ADEPT® (n=203)	LRS (n=199)	p-value*
Reformed adhesions			
Number of sites with reformed adhesions (mean ± s.d.)	4.92 ± 3.91	5.11 ± 4.12	0.722
Number of sites without reformed adhesions (mean ± s.d.)	3.77 ± 2.72	3.32 ± 2.29	0.065
% patients with at least one	87.7%	86.9%	0.832
***De novo* adhesions**			
Number of sites with at least one *de novo* adhesion (mean ± s.d.)	1.13 ± 1.65	1.29 ± 1.61	0.036
% patients free of *de novo* adhesions	52.7%	42.7%	0.029
Abdominal wall adhesions			
Change from 1st to 2nd look in number of sites (mean ± s.d.)	-1.17 ± 1.63	-0.94 ± 1.60	0.184
% patients with reduction from 1st to 2nd look in no. sites	65.5%	58.3%	0.129
Visceral adhesions			
Change from 1st to 2nd look in number of sites (mean ± s.d.)	-1.47 ± 2.62	-1.07 ± 2.22	0.046
% patients with reduction from 1st to 2nd look in no. sites	68.5%	63.3%	0.228

* not adjusted for multiplicity.

Table 8: Pivotal Study Secondary Effectiveness Endpoints (PP) for Subgroup of Patients with a Primary Diagnosis of Pelvic Pain

Endpoint / Variable	ADEPT® (n=118)	LRS (n=108)	p-value*
VAS score for pelvic pain			
Change from screening to 2nd look for patients with a primary diagnosis of pelvic pain (mean ± s.d.)	-35.8 ± 32.8	-30.8 ± 30.2	0.995

* not adjusted for multiplicity.

V. DIRECTIONS FOR USE

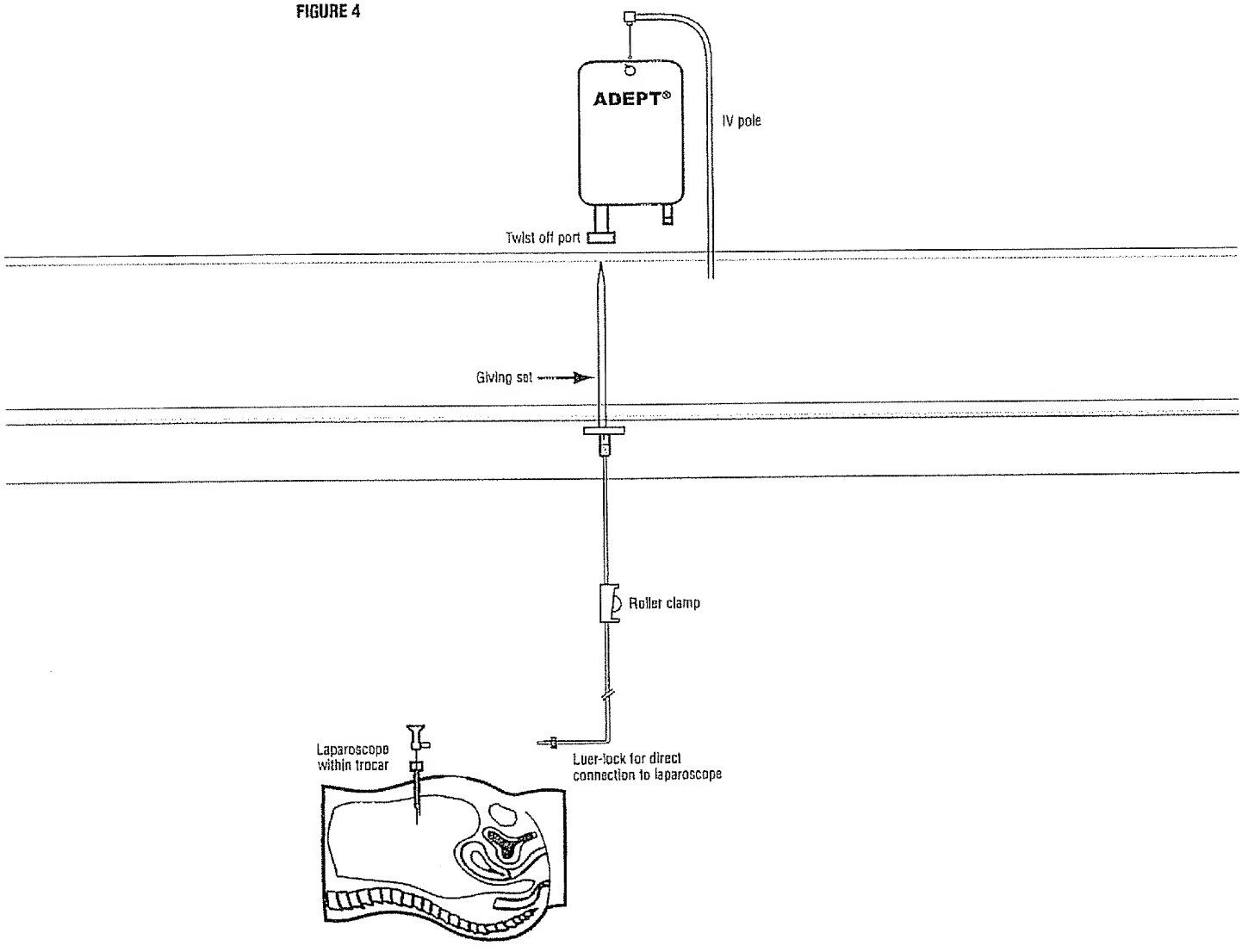
ADEPT® is administered directly into the peritoneal cavity during laparoscopic gynecological surgery, being used as an irrigant solution during the course of surgery. Once the surgeon has completed the surgical procedure(s), the cavity is aspirated of all remaining fluid. A final volume of 1 liter of ADEPT® is then introduced into the cavity before removal of the scope

Using standard operating room technique:

1. ADEPT® should be warmed to approximately body temperature prior to use, using a device specifically intended for warming solutions in operating rooms
2. Remove the outer wrap from the ADEPT® bag and hang the sterile bag of solution on an I.V. pole
3. Remove the twist-off tab from the spike port and insert a giving set for connection to a laparoscope.
4. ADEPT® should be used intra-operatively as an irrigant solution, and as a post-operative instillate. The solution will flow through a giving set and through laparoscopes.
5. When used as an intra-operative irrigant solution, at least 100 mL of ADEPT® should be introduced to the cavity every 30 minutes
6. Remove remaining fluid before introducing the final instillation
7. For the final instillation of ADEPT®, prior to removal of the laparoscope, one liter (a new bag of ADEPT® if 1 liter bags are being used) should be used. Direct the solution at the operative sites in the first instance, the remainder being distributed throughout the cavity.
8. Dispose of the bag and any unused portion of the solution following normal operating room biological hazard procedures

SEE FIGURE 4

FIGURE 4



HOW SUPPLIED

ADEPT® is packaged in single use, flexible polyvinylchloride bags, fitted with connecting ports, containing 1 liter or 1 5 liters of solution The product is presented sterile (by heating in an autoclave). The bags are packaged in cartons of 10 x 1 liter or 5 x 1 5 liters.

STORAGE

ADEPT® should not be stored above 30°C. Do not refrigerate or freeze

ADEPT® may be kept in a warming device for up to 14 days, provided it is not removed and then replaced back in the warming device. At all other times, storage below 4°C or above 30°C is not recommended.

References:

1 Hosie K, Gilbert JA, Kerr D, Brown CB, Peers EM Fluid dynamics in man of an intraperitoneal drug delivery solution: 4% Icodextrin Drug Deliv 2001; 8: 9-12

2 Moberly JB et al , Pharmacokinetics of Icodextrin in peritoneal dialysis patients Kidney International 62, Suppl.81, 2002, S23-S33.

3 Sutton C, Minelli L, Garcia E et al Use of Icodextrin 4% solution in the reduction of adhesion formation after gynaecological surgery. Gynecological Surgery 2005; 2(4): 287-296.

4 Menzies D, Hidalgo M, Walz MD et al Use of Icodextrin 4% solution in the prevention of adhesion formation following general surgery Annals of the College of Surgeons of England 2006; 88 (4): 375-382

Manufactured for:
Baxter Healthcare Corporation
Deerfield, IL 60015 USA

6208501EH01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 10

Research Update (M.L. Laboratories)

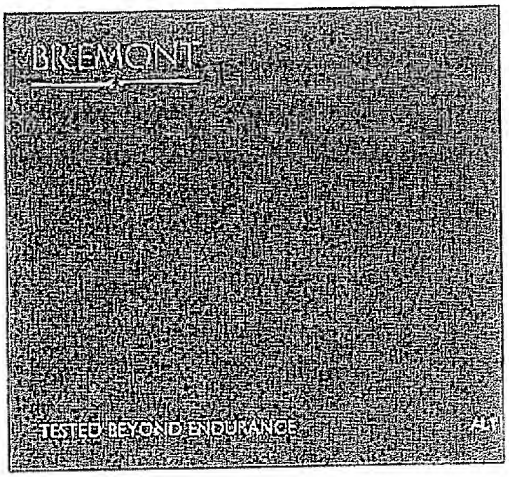
Date : 04/04/2005 @ 12:00

Source : UK Regulatory (RNS and others)

Stock : M.L. Laboratories (MLB)

Quote : ₀ 9.183 0 0 (0.00%) @ 06:00

<< Back Quote Chart Trades Level2



Research Update (M.L. Laboratories)

RNS Number:5401K
M.L. Laboratories PLC
04 April 2005

ML Laboratories PLC

Presents Phase III Trial Data on Adept(R) and Hosts Symposium on Reduction of Surgical Adhesions at London Gynecologic Endoscopy Congress

St Albans, UK, 4 April 2005 - ML Laboratories PLC (LSE: MLB) is today presenting data from the first ever double-blind, randomised, study in abdominal surgery with Adept at the 14th Annual Congress of the International Society of Gynecologic Endoscopy in London. The Company is also hosting a symposium on the need for improved adhesion reduction agents in abdominal surgery, with presentations from some of the world's leading opinion leaders in gynaecological adhesions.

Use of many available adhesion reduction agents has generally been limited due to cost, safety issues and technical difficulties, especially in abdominal surgery. Available in Europe since 2000, Adept is a 4% icodextrin solution that has been used in adhesion reduction in over 100,000 surgical patients. Benefits over existing treatments include cost-effectiveness and ease of use, particularly where there have been deficiencies with other anti-adhesion agents.

Prof Gere diZerega, MD, Professor of Obstetrics and Gynecology at the Los

Angeles County University of Southern California, USA, will present data from the 440 patient, pivotal Phase III trial, which examined the efficacy of Adept in a comparative study. The results of this landmark study will be submitted to the Food and Drug Administration for US marketing authorisation in the coming months.

Geoffrey Trew, MRCOG, Consultant in Reproductive Medicine and Surgery at Hammersmith Hospital, London, UK, will consider the risk of adhesion-related problems to a patient and the practical implementation of adhesion prevention in routine surgery.

Adrian Lower, FRCOG, Consultant Gynaecologist for the London Clinic, London, and Medical Director of the ISIS Fertility Centre, Colchester, UK will review recent findings from an epidemiological study, which identifies gynaecological surgical procedures, related diseases and other factors defining high-risk populations at whom anti-adhesion strategies should be targeted routinely.

Commenting, Geoff Trew, MRCOG, said:

"This is biggest and best constructed study ever undertaken with an anti-adhesion agent and I find the results very exciting. Adept is one of the most important surgical device developments in the last decade, filling a niche where there is currently really nothing at all. It is safe, easy to use and inexpensive, and these study results have confirmed what many people suspected - that is an effective agent."

A copy of the presentations from today's symposium is available on request.

Contacts:

ML Laboratories plc Tel: +44 (0)1727 837 341

Paul Ballington, Director of Marketing & Business Development

Financial Dynamics Tel: +44 (0) 20 7831 3113

Sarah MacLeod

Notes to Editors

ML Laboratories plc

ML operates through two divisions, both focused on the development of high value pharmaceutical products - Innovata Biomed, the Group's respiratory division, and ML Pharmaceuticals, a pharmaceutical product development business.

Innovata Biomed (IB) is a leading independent provider of inhaled drug delivery technologies to the global pharmaceutical industry, formulating dry powders and developing proprietary inhaler systems through to full industrialisation. IB's proven delivery technologies are available for proof-of-principle testing and as

fast-to-market drug delivery solutions. It has a number of respiratory products both in development and marketed by pharmaceutical company licensees including Celltech, Otsuka and Pliva.

ML's pharmaceutical product development division, ML Pharmaceuticals, contains both marketed products and new therapeutics in clinical development. Marketed products include Extraneal for the treatment of renal failure, which has been licensed to Baxter, and Adept for the reduction of adhesions in abdominal surgery, which is marketed by Shire Pharmaceuticals in Europe. New therapeutic products in development include Alpharen, a phosphate binder to assist the management of kidney failure, treatments for prostate and skin cancer and a pain management compound.

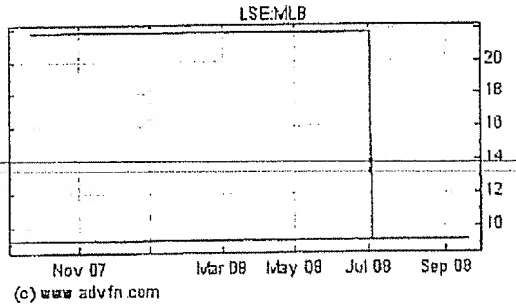
This information is provided by RNS
The company news service from the London Stock Exchange

END

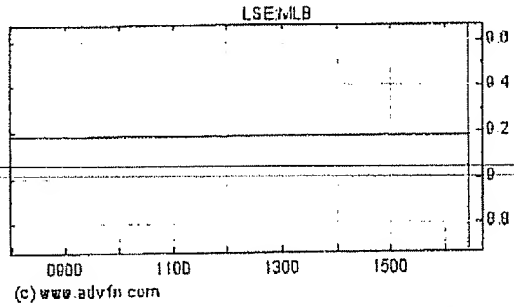
RESPKQKBKBKDKQK

<< Back

M.L. Laboratories Historical Chart



M.L. Laboratories Intraday Chart



LSE and PLUS quotes are live NYSE and AMEX quotes are delayed by at least 20 minutes
All other quotes are delayed by at least 15 minutes unless otherwise stated.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 11

New study finds ADEPT® effective in reducing Adhesions following Gynecological Laparoscopic Surgery

1 November 2007

New study finds ADEPT® effective in reducing Adhesions following Gynecological Laparoscopic Surgery

- Anti-adhesion agent may reduce infertility due to adhesions after surgery -

DEERFIELD, Ill., and CHIPPENHAM UK, November 1, 2007 — Baxter International Inc. (NYSE: BAX) and Vectura Group plc (LSE: VEC) today announced publication of data in the November 2007 issue of *Fertility and Sterility* of the first randomized, double-blind trial of an adhesion reduction agent, ADEPT Adhesion Reduction Solution [4% Icodextrin Solution] in gynecological laparoscopic surgery compared to lactated Ringer's solution (LRS). In one of the largest adhesion reduction agent trials performed, ADEPT was shown to be more effective than lactated Ringer's solution (LRS) in reducing the incidence of post-operative adhesions in patients undergoing gynecological laparoscopic adhesiolysis. ADEPT was also found to be safe and in particular showed efficacy in infertility patients.

"Adhesions can take several days to form following surgery," said Ron Lloyd, vice president of Baxter's BioTherapeutics and Regenerative Medicine business. "Other solutions used, although not approved, for adhesion reduction during laparoscopic gynecological surgery are absorbed within hours, reducing their effectiveness in preventing adhesions. ADEPT forms a fluid reservoir in the peritoneal cavity that resides there during the critical period of adhesion formation, separating and minimizing contact between organs."

Adhesions are abnormal fibrous attachments between tissues or organs that develop following pelvic or abdominal surgery. The incidence of adhesion formation has increased with the rise in gynecological surgery, and it has been shown that between 60 and 90 percent of women suffer post-operative adhesions following major gynecological procedures. Pelvic factors such as adhesions account for between 20 and 40 percent of infertility cases in women and can cause other complications, increasing patient morbidity and healthcare costs.

"Increased use of laparoscopic surgery as an alternative to open surgery has helped reduce post-operative adhesions, but they remain a major problem," said Dr. Tom Lyons, MD, director Center of Women's Care and Reproductive Surgery and Clinical Assistant Professor, Dept. of OB/GYN, Emory University Medical School. "Solutions used to address adhesions in the past have been largely ineffective, and none have been approved by the FDA for use in laparoscopic procedures. An effective adhesion-reduction agent like ADEPT that is approved for use in laparoscopic procedures provides a major clinical benefit."

The study, conducted by Innovata Ltd, now part of Vectura Group plc, involved more than 400 patients at 16 sites in the United States. Two hundred and three patients undergoing gynecological laparoscopic surgery involving adhesiolysis were administered ADEPT during surgery and 199 patients were administered LRS. Patients' primary diagnoses included pelvic pain, infertility, endometriosis and known adhesions. A second follow-up laparoscopy was scheduled four to eight weeks later.

Among patients in the ADEPT group, more than 45 percent achieved "clinical success" during the second physician observation compared to 35 6 percent in the LRS group (Intent to Treat population). Clinical success was defined as the greater of a reduction in adhesions of at least three or 30 percent of sites lysed between the first and second laparoscopies. Among infertility patients, 52.9 percent of patients in the ADEPT group had a positive reduction in American Fertility Score (AFS), the standardized method to score and classify adhesions to the ovaries or fallopian tubes that may affect fertility, compared to 30.4 percent in the LRS group (*per protocol* population).

ADEPT is a four percent icodextrin solution that has been approved for adhesion reduction in Europe since 2000, and since July 2006 in the United States for gynecological laparoscopic procedures involving adhesiolysis ADEPT is the first and only anti-adhesion agent approved for use in laparoscopic surgery in the United States. As a fluid, ADEPT is easy to use in laparoscopic procedures, as it can be delivered directly and rapidly through a laparoscopic port during surgery. Innovata Ltd (part of Vectura Group plc) conducted the study as part of the ADEPT development program before licensing ADEPT to Baxter in January 2006. ADEPT is part of Baxter's Regenerative Medicine business unit within the BioScience division. The Regenerative Medicine business unit also sells products used in hemostasis, wound sealing and tissue regeneration, and products used in adult stem-call therapies.

About ADEPT

ADEPT Adhesion Reduction Solution is indicated for use intraperitoneally as an adjunct to good surgical technique for the reduction of post-surgical adhesions in patients undergoing gynecological laparoscopic adhesiolysis.

ADEPT is for direct intraperitoneal administration only **NOT** for intravenous (IV) administration. ADEPT is contraindicated in patients with known or suspected allergy to cornstarch based on polymers, e.g., icodextrin, or with maltose or isomaltose intolerance, or with glycogen storage disease. ADEPT is contraindicated in laparotomy, in cases involving bowel resection or repair, or appendectomy and in surgical cases with frank abdomino-pelvic infection.

There have been rare reports of sterile peritonitis following the use of icodextrin. Leakage of ADEPT from port sites may lead to wound healing complications; meticulous fascial closure may reduce leakage through laparoscopic port sites post-operatively. There have been rare reports of hypersensitivity reactions, pulmonary edema, pulmonary effusion and arrhythmia. Anaphylaxis has been reported in a few patients. Maltose metabolites of icodextrin may interfere with blood glucose measurement in diabetic patients who use rapid blood glucose systems that are not glucose specific.

In the pivotal study, the most frequently occurring treatment-related adverse events between surgeries were post-procedural leaking from port sites, labial, vulvar or vaginal swelling and abdominal distention.

RX Only: For safe and proper use of this device, please refer to full device "Instructions For Use."

About Baxter International

Baxter International Inc., through its subsidiaries, assists healthcare professionals and their patients with the treatment of complex medical conditions, including hemophilia, immune disorders, cancer, infectious diseases, kidney disease, trauma and other conditions. The company applies its expertise in medical devices, pharmaceuticals and biotechnology to make a meaningful difference in patients' lives.

About Vectura

Vectura is a pulmonary drug development company focused principally on the development of a range of inhaled therapies for the treatment of respiratory and neurological diseases. Vectura develops products to treat respiratory diseases such as asthma, COPD and cystic fibrosis. The Company also targets opportunities where optimized delivery via the lungs into the blood stream can provide significant benefits, such as a rapid onset of action, improved efficacy and improved tolerability compared with current therapies. Vectura has eight marketed products and a portfolio of drugs in clinical and pre-clinical development, some of which have been licensed to major pharmaceutical companies. The Company also seeks to develop certain programmes further through development to optimise value at a later licensing stage. Vectura also offers its formulation and inhalation technologies to other pharmaceutical companies on a licensing basis where this complements Vectura's business strategy.

Vectura has development collaborations with a broad range of pharmaceutical companies including Boehringer Ingelheim, Novartis and Chiesi. The acquisition of Innovata in January 2007 brought established alliances with a number of additional companies, such as Baxter, GSK, Merck Generics (part of Mylan Inc), UCB and Otsuka as well providing revenue streams, complementary products and critical mass.

For further information, please visit Vectura's website at www vectura.com

ADEPT is a registered trademark of Innovata Ltd.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 12

Innovata plc announces Baxter International Inc. as global licensee for Adept® Adhesion Reduction Solution

03 Jan 2006

Innovata plc announces Baxter International Inc. as global licensee for Adept® Adhesion Reduction Solution

Nottingham, UK, 3 January 2006 - Innovata plc (LSE: IOV), the pulmonary product company, today announced that it has granted Baxter International Inc. a global licence for Adept, its adhesion reduction solution for use in abdominal, obstetric and gynaecologic surgery.

Adept is an icodextrin solution that was developed by Innovata and previously licensed to Shire Pharmaceuticals in Europe. The product is currently being reviewed by the Food and Drug Administration (FDA) for U.S. marketing approval and the outcome of the review is expected during the second half of 2006.

Adept will be marketed by Baxter's BioSurgery business, a business unit that is focused on developing and commercializing novel biomaterials such as Tisseel®, a fibrin based adhesive for tissue repair, FloSeal® for rapid haemostasis, and CoSeal®, a vascular sealant.

Under the terms of this new agreement, Baxter will take over the sales and marketing of Adept effective January 2006. Innovata remains responsible for obtaining U.S. approval for Adept, while Baxter is responsible for obtaining approval in other markets, including Japan. Financial terms were not disclosed.

Kieran Murphy, Chief Executive Officer of Innovata, commented, "We are delighted to be concluding this agreement with Baxter, given the company's knowledge of icodextrin, strength in the hospital sales markets and global presence. Baxter can now capitalise on the results of the U.S. pivotal study to increase sales in Europe and eventually worldwide. Baxter's European marketing efforts will begin in earnest in January and we look forward to a roll-out of Adept in the U.S. and other markets in the months to follow."

"We believe this technology offers significant potential for growth globally and addresses a market that has been underserved for some time," said Gordon Sutherland, General Manager of Baxter's BioSurgery business. "This agreement adds another platform technology to our BioSurgery portfolio and allows us to enter the anti-adhesion market segment with a clinically proven product."

There will be a conference call for analysts today at 9.30am GMT. Please contact Mo Noonan at Financial Dynamics on 020 7269 7116 for details.

ENDS

Contacts:

Innovata plc
Tel: 0115 974 474

Kieran Murphy, Chief Executive Officer
Paul Ballington, Director of Commercial Operations

Financial Dynamics
Tel: 020 7831 3113
Sarah MacLeod / John Gilbert

Notes to Editors:

About Innovata plc

Innovata plc specialises in the development of pulmonary products for the treatment of respiratory disorders and other serious diseases. Using its proprietary dry powder inhaler and drug formulation technologies, Innovata plc has developed a substantial portfolio of 13 marketed and clinical-stage products and has partnered with a number of pharmaceutical companies including Baxter, Merck KGaA, Celltech (part of UCB) and Otsuka.

Innovata plc was formed in July 2005 when ML Laboratories PLC acquired Quadrant Technologies Limited. The company has over 90 employees of whom 65 are engaged in research and development, mainly based at Innovata's headquarters in Ruddington, Nottingham, United Kingdom. The Company is listed on the London Stock Exchange under the symbol IOV.

Adept

A number of physical barriers have been developed for use during surgery to help prevent adhesions. However, these have had limited uptake in open surgery and are generally difficult to use in laparoscopic surgery. One key challenge is that these physical barriers (gels, sprays or film-like sheets placed between neighbouring organs in the peritoneal cavity) may reduce adhesions where they are placed, but do not prevent adhesions developing elsewhere in the abdomen. The ideal adhesion-reduction agent should be easy to use in all types of surgical procedure and capable of reducing adhesion formation at the operating site and throughout the peritoneum. Ongoing research suggests that Adept® (icodextrin 4%) may be closest to this ideal profile. A non-viscous liquid, Adept can be used for both open and laparoscopic surgery, and is compatible with a wide range of antibiotics used during and after surgery. Adept is simple to use, being instilled slowly at the end of surgical procedures and used during surgery as an irrigant with a 1.5 litre bag of Adept (enabling 500ml to be used during procedures with 1000ml remaining for instillation at the end of surgery).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 13

Print

ML Laboratories PLC (MLB.L) Milestone Payment And Return Of Adept Marketing Rights In Europe
10/19/2005 5 09.20 PM

St Albans, UK, 21st June 2005 -- ML Laboratories plc (LSE: MLB) today announces that, with effect from 30 December 2005, Shire Pharmaceuticals will return to ML all its rights to market Adept, ML's adhesion reduction solution. The return of marketing rights to ML has arisen as a result of a change in Shire's strategic focus. ML is now reviewing the future marketing of Adept in Europe as well as continuing licensing discussions for the US and Japan, as previously announced.

ML successfully launched Adept for the reduction of adhesions following abdominal surgery in the UK in May 2000 and licensed Europe-wide rights to Shire in October 2001. Since then, Shire has launched Adept across all the key EU markets and has entered agreements to distribute the product in other EU countries. Adept currently has sales of $5m per annum.

In line with the terms of the agreement, ML is due to receive a payment from Shire in relation to the Adept pivotal study in the US ("the PAMELA study"). Data from the PAMELA study, announced on 6 December 2004, will form the basis for the Adept Marketing Authorisation Application to the US Food and Drug Administration (FDA), expected in the coming months.

The return of rights from Shire enables ML to consider a number of possible options, including continued licensing of Adept on a regional or global basis. ML is also reviewing the opportunity to return to marketing the product directly within the EU. ML hopes to make further announcements about the licensing and marketing of Adept in the near future.

Joseph Rus, Executive Vice President and General Manager, International at Shire Pharmaceuticals PLC commented:

"Following a change in our strategic priorities after a review of our business last year, we have decided to return to ML all Shire's rights to market ADEPT. We are proud of the success we have brought to ADEPT and wish ML Laboratories future success with the brand. "

Kieran Murphy, Chief Executive Officer of ML, said: "ML recognises that Shire has been a most able partner over the past three years, having significantly raised awareness among surgeons of the need to consider adhesion prevention strategies with Adept when carrying out abdominal surgery. The new clinical data from our pivotal US Phase III study, will drive opportunities for ML to consider a number of options for Adept which will reflect the Group's future strategic direction."

Contacts:

ML Laboratories plc Tel: 01727 739300 Kieran Murphy, Chief Executive Officer Paul Ballington, Director of Marketing & Business Development

Financial Dynamics Tel. 020 7831 3113 Julia Phillips / David Yates

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 14

FDA panel recommends approval of ADEPT® Adhesion Reduction Solution

28 Mar 2006

FDA panel recommends approval of ADEPT® Adhesion Reduction Solution

Nottingham, UK, 28th March 2006 – Innovata plc (LSE: IOV) today announces that its ADEPT® adhesion reduction solution, for use in obstetric and gynecologic surgery, received a unanimous recommendation for marketing approval by the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee of the US Food and Drug Administration (FDA).

The FDA advisory panel has recommended that ADEPT should be indicated as an adjunct to good surgical technique for the reduction of post-surgical adhesions in patients undergoing gynaecologic laparoscopic surgery which includes adhesiolysis.

Professor Dan Martin, from the University of Tennessee, Center for the Health Sciences, one of the lead investigators in the pivotal Phase III trial of ADEPT and former President of the American Association of Gynecologic Laparoscopists, said:

"We welcome the US FDA advisory panel's recommendation which helps to pave the way for the benefits of ADEPT to be seen by surgeons and patients across the USA. More than two million OB/GYN procedures are performed annually in the USA, including approximately 500,000 gynecologic laparoscopic procedures ADEPT has the potential to reduce the number of adhesion-related complications, which can lead to hospitalisation and even infertility, in women undergoing such procedures."

Available in Europe since 2000, ADEPT is a 4% icodextrin solution that has been used in adhesion reduction in over 100,000 surgical patients. The Phase III study supporting Innovata's filing submission was conducted in over 400 patients undergoing gynecological laparoscopic adhesiolysis in the USA. The results showed that ADEPT reduced the number of adhesions following surgery as well as reducing pain scores while the overall incidence of adverse events in the ADEPT and control groups was similar.

ADEPT is licensed to Baxter International Inc. on a global basis under an agreement formed in January 2006. ADEPT is marketed by Baxter's BioSurgery business, a business unit that is focused on developing and commercializing novel biomaterials and biosurgery products.

Kieran Murphy, Chief Executive Officer of Innovata, said:

"ADEPT is one of the most important surgical device developments in the last decade, filling a niche where there are limited options. The positive review by the FDA advisory panel brings us closer to approval of ADEPT in the USA and, should it be successful, it will strengthen the product's market position in Europe and support the regulatory approval process in additional markets, including Japan."

Contacts:

Innovata plc

Tel: 0115 974 7474
Kieran Murphy, Chief Executive Officer
Peter Shennan, Finance Director

Financial Dynamics
Tel: 020 7831 3113
Sarah MacLeod / John Gilbert

Notes to Editors

About Adhesions

An adhesion is a band of scar tissue that binds two planes of tissue together which should remain separate. Studies suggest that adhesions may form in over 10% of patients who have never had surgery and in 93% of patients having abdominal or pelvic surgery[1] . Pelvic and abdominal adhesions are a significant women's health issue as they can be associated with infertility, small bowel obstruction and chronic pelvic pain.

The use of anti-adhesion products has been limited by their difficulty in use and lack of clinical efficacy data [2].

About Innovata plc

Innovata plc specialises in the development of pulmonary products for the treatment of respiratory disorders and other serious diseases. Using its proprietary dry powder inhaler and drug formulation technologies, the company has developed a pipeline of revenue-generating/marketed and clinical-stage products. In addition, the Company has a portfolio of non-pulmonary products with growing revenues. Innovata has established development and marketing partnerships with a number of pharmaceutical companies including Baxter, Merck KGaA, UCB and Otsuka.

Innovata was formed in July 2005 when ML Laboratories PLC acquired Quadrant Technologies Limited and the remaining minority interest in Innovata Biomed Limited. The company has over 90 employees of whom of 65 are engaged in research and development, mainly based at Innovata plc's headquarters in Rudding

1 Menzies, D. and Ellis, H. (1990) Intestinal obstruction from adhesions—How big is the problem? Ann. R. Coll. Surg. Engl., 72, 72–60.
2 Frost and Sullivan, March 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 15

FDA Issues Approvable Letter for ADEPT® Adhesion Reduction Solution

01 Jun 2006

FDA Issues Approvable Letter for ADEPT® Adhesion Reduction Solution

Nottingham, UK, 1st June 2006 – Innovata plc (LSE: IOV) today announces that the FDA has issued a letter to the company indicating that ADEPT® adhesion reduction solution is approvable for use as an adjunct to good surgical technique for the reduction of post surgical adhesions in patients undergoing gynecological laparoscopic adhesiolysis.

On March 27th 2006, ADEPT received a unanimous recommendation for marketing approval by the Obstetrics and Gynecology Devices Panel of the US Food and Drug Administration (FDA)

The letter states that the FDA is continuing to review the product labeling and requires Innovata to submit amended label copy for adverse event data and warnings and also to agree proposals for post-approval safety monitoring. Innovata plans to submit this information as quickly as possible.

Kieran Murphy, Chief Executive Officer of Innovata, said: "We are delighted by this news and hope to complete the approval process in the shortest possible time."

Available in Europe since 2000, ADEPT is a 4% icodextrin solution that has been used in adhesion reduction in over 100,000 surgical patients. The Phase III study supporting Innovata's filing submission was conducted in over 400 patients undergoing gynecological laparoscopic adhesiolysis in the USA. The results showed that ADEPT reduced the number of adhesions following surgery while the overall incidence of adverse events in the ADEPT and control groups was similar.

ADEPT is licensed to Baxter International Inc. on a global basis under an agreement formed in January 2006. ADEPT is marketed by Baxter's BioSurgery business, a business unit that is focused on developing and commercializing novel biomaterials and biosurgery products.

Contacts:
Innovata plc
Tel: 0115 974 7474
Kieran Murphy, Chief Executive Officer
Peter Shennan, Finance Director

Financial Dynamics
Tel: 020 7831 3113
David Yates/ Anna Keeble

Notes to Editors
About Adhesions
An adhesion is a band of scar tissue that binds two planes of tissue together which should remain separate. Studies suggest that adhesions may form in over 10% of patients who have never had surgery and in 93% of patients having abdominal or pelvic surgery [1]. Pelvic and abdominal adhesions are a significant women's health issue as they can be associated with infertility, small bowel obstruction and chronic pelvic pain.

The use of anti-adhesion products has been limited by their difficulty in use and lack of clinical efficacy data [2].

About Innovata plc
Innovata plc specialises in the development of pulmonary products for the treatment of respiratory disorders and other serious diseases. Using its proprietary dry powder inhaler and drug formulation technologies, the company has developed a pipeline of revenue-generating/marketed and clinical-stage products In addition, the Company has a portfolio of non-pulmonary products with growing revenues. Innovata has established development and marketing partnerships with a number of pharmaceutical companies including Baxter, Merck KGaA, UCB and Otsuka.

Innovata was formed in July 2005 when ML Laboratories PLC acquired Quadrant Technologies Limited and the remaining minority interest in Innovata Biomed Limited. The company has over 90 employees of whom of 65 are engaged in research and development, mainly based at Innovata plc's headquarters in Ruddington.

1 **Menzies**, D. and **Ellis**, H. **(1990)** Intestinal obstruction from adhesions—How big is the problem? Ann. R. Coll. Surg. Engl., 72, 72–60
2 Frost and Sullivan, March 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 16

<< Back to News Releases

2008 Archives
2007 Archives
2006 Archives
2005 Archives
2004 Archives
2003 Archives
2002 Archives
2001 Archives

News Release

Home > About Baxter > News Room > News Releases > ..

Baxter Expands BioSurgery Product Portfolio with FDA 510(K) Marketing Clearance for TricOs™ T Bone Void Filler

Tricos T Represents Baxter's First Commercially Available Orthobiologic Product in the United States

DEERFIELD, Ill., January 9, 2006 – Baxter Healthcare Corporation announced today it has received marketing clearance from the U.S. Food Drug Administration (FDA) for TricOs™ T Bone Void Filler, which is indic for voids or gaps in bone that are not intrinsic to the stability of the bony structure, including bone defects from surgery or traumatic injury. The clearance of TricOs T further expands Baxter's BioSurgery product portfo and represents the company's first commercially available orthobiologic product in the United States.

"TricOs T is an alternative technology to harvesting bone from the patient certain spinal and orthopedic surgeries," said Gordon Sutherland, genera manager of Baxter's BioSurgery business. "Bone harvesting from the pat can increase post-operative pain and the risk of infection."

TricOs T is a proprietary combination of hydroxyapatite-coated beta tricalcium phosphate (HA/TCP) granules and a fibrin matrix based on Baxter's TISSEEL ® VH [Fibrin Sealant] contained in one convenient kit. TricOs T provides a three-dimensional osteoconductive environment for t formation of new bone. The product is also biocompatible, allowing it to b resorbed by the body over time

"Early users of this technology have stated that they like the handling characteristics of the product as it is very easy to mold into the correct sh to fit the bone defect," Sutherland added.

The company expects full market availability for the product in the United States to occur in the second half of 2006.

Baxter's BioSurgery business is focused on developing and commercializ novel biomaterials for hemostasis and hard and soft tissue repair in surge In addition to TISSEEL, other products in the BioSurgery portfolio include FLOSEAL® [Hemostatic Matrix] for rapid hemostasis, and COSEAL® [Surgical Sealant], a vascular sealant. With annual sales of approximatel $250 million, BioSurgery has become one of Baxter's fastest growing businesses.

The company's accelerated investments in this business have resulted ir recent research and development collaborations, including an agreemen signed this month with Innovata PLC to acquire a global license for Adep an adhesion reduction solution for use in obstetric and gynecologic surge

Baxter also announced a major follow-on research and commercializatio agreement with Kuros AG in November, which includes the development a variety of biomaterials addressing hard and soft tissue repair. This research agreement includes future enhancements to the TricOs T produ

Baxter Healthcare Corporation is the principal U.S. operating subsidiary Baxter International Inc. (NYSE: BAX). Baxter assists healthcare

professionals and their patients with treatment of complex medical conditions, including cancer, hemophilia, immune disorders, kidney disea and trauma. The company applies its expertise in medical devices, pharmaceuticals and biotechnology to make a meaningful difference in patients' lives. For more information about Baxter, please visit www.baxter.com.

This release includes forward-looking statements concerning the timing c full market availability of the product, the company's collaboration with Ku and future product development involving biomaterials. The statements a based on assumptions about many important factors, including the follow which could cause actual results to differ materially from those in the forward-looking statements: successful scale-up of operations; clinical developments relating to the existing product and future products; receip all necessary regulatory approvals; and other risks identified in the company's most recent filing on Form 10-Q. The company does not undertake to update its forward-looking statements.

For Additional Information

Media Contacts:
Amy Cynkar, (847) 940-5166
Deborah Spak, (847) 948-2349

Investor Contacts:
Mary Kay Ladone, Baxter, (847) 9
3371
Clare Sullivan, Baxter, (847) 948-3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

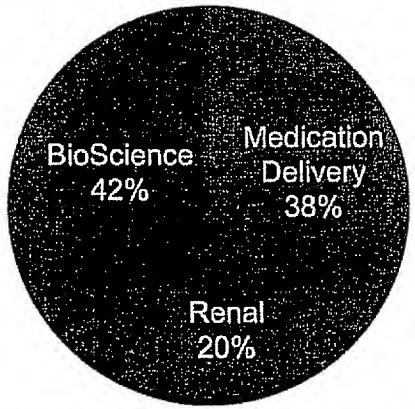
TAB 17

Goldman Sachs
Global Healthcare Conference
September 4, 2008

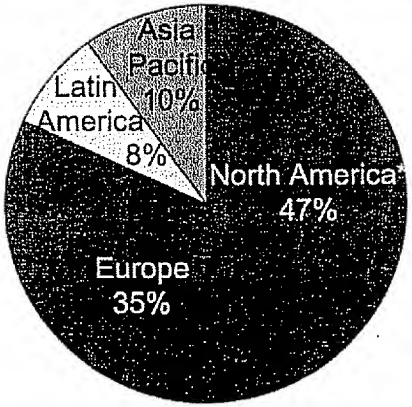
Baxter

An Established And Diversified Global Healthcare Leader

2007 Sales by Business



2007 Sales by Region

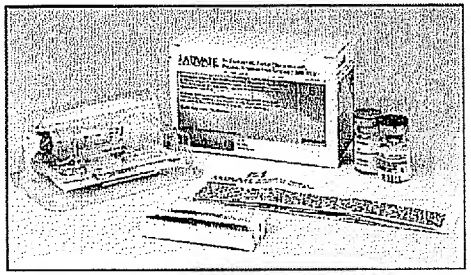


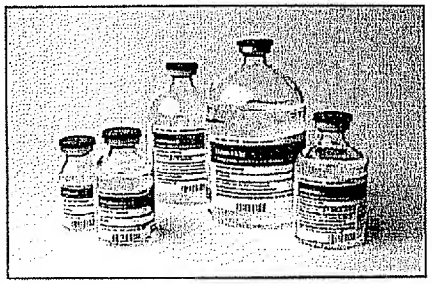
2007 Total Baxter Sales = $11.3 Billion

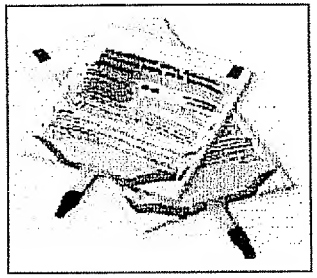
- Leveraging capabilities across businesses to create synergies
- Deriving over 70% of revenues from products in market-leading positions
- Extremely strong image and reputation driven by Baxter brand
- Strong global infrastructure and channel strength
- Expanding access to medically necessary products that address unmet needs

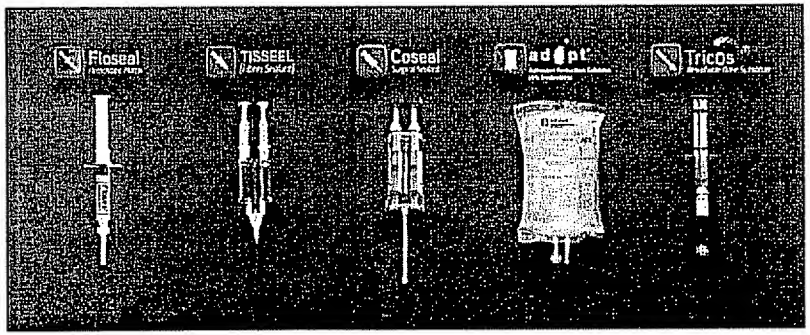
*United States and Canada

BioScience









BioScience
2007 Sales = $4.6 Billion

- Recombinant Proteins
- Plasma-Based Products
- Regenerative Medicine / BioSurgery
- Vaccines

2006 - 2011 Sales Growth* = 7% - 9% CAGR

- Driving improved mix with differentiated products (ADVATE, Liquid IVIG, Flexbumin)
- Balancing plasma supply and demand
- Growing specialty therapeutics (Aralast, BioSurgery, FEIBA)

Sustainable Growth And Profitability In BioScience

Baxter

*Excluding Foreign Currency

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Colin Brown
Serial No.: 09/700,057
Filed: February 5, 2001

Confirmation No: 1282
Group Art Unit: 1623
Examiner: Everett White

For: *SURGICAL COMPOSITIONS AND METHODS FOR USING THE SAME*

TAB 18

New Device Approval

Adept® Adhesion Reduction Solution (4% Icodextrin) - P050011

This is a brief overview of information related to FDA's approval to market this product. See the links below to the Summary of Safety and Effectiveness and product labeling for more complete information on this product, its indications for use, and the basis for FDA's approval.

Product Name: Adept® (4% Icodextrin) Adhesion Reduction Solution
PMA Applicant: Innovata plc
Address: 104a West Street, Farnham, Surrey, GU9 7EN, United Kingdom
Approval Date: July 28, 2006
Approval Letter: http://www.fda.gov/cdrh/pdf5/p050011a.pdf

What is it? Adept® Adhesion Reduction Solution (4% Icodextrin) is a pale yellow fluid that contains icodextrin. The fluid is used during or after laparoscopic gynecological surgery to separate and protect tissues and decrease the number of new adhesions after surgery. Adept® is supplied sterile, in a single-use bag.

How does it work? During surgery, and/or at the end of surgery, the tissues in the abdomen are covered with the Adept® fluid to provide a temporary, physical separation of the tissue surfaces during the early phases of the natural healing process.

When is it used? Adept® is used in patients undergoing laparoscopic gynecological surgery (surgery on the female reproductive organs, e.g., ovaries, uterus, fallopian tubes) to reduce the amount or severity adhesions (scar tissue that binds together normally separate tissues) in the abdomen. The fluid is used during surgery and/or placed in the abdomen at the end of the surgery, to separate and protect tissues, decreasing the number of new adhesions after surgery.

What will it accomplish? Adept® will reduce the chance that a woman will develop adhesions following laparoscopic surgery. Adhesions are a common complication of gynecological surgery, and can be the cause of pelvic pain, bowel obstruction, or infertility.

When should it not be used? Adept® should not be used in patients

- with known or suspected allergy to cornstarch based polymers e.g., icodextrin, with maltose or isomaltose intolerance, or with glycogen storage disease;
- with frank infection (e.g. peritonitis) in the abdomino-pelvic cavity;
- in procedures involving laparotomy incision. (Serious post-operative wound complications including dehiscence and cutaneous fistula formation have been reported from clinical experience outside the US when Adept® was used in surgical cases with laparotomy incision);
- in procedures involving bowel resection or repair, or appendectomy. (Anastomotic failure, ileus and peritonitis following procedures involving bowel resection and instillation of Adept® have been reported from clinical experience outside of the US.)

Additional information: The Summary of Safety and Effectiveness and labeling will be available at: http://www.fda.gov/cdrh/pdf5/p050011.html

Updated August 28, 2006
